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THE NEUROLOGICAL EFFECTS OF INH

BY

MAJ J. E. Jordan, MC
Mr. Stephen Shields
Mr. Dan Bochneak

December 1971

U. S. ARMY AEROMEDICAL RESEARCH LABORATORY

Fort Rucker, Alabama

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II

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APPROVED: ROBERT W. BAILEY
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INTRODUCTION

For several years the drug isoniazid (INH) has been employed in the therapeutic and prophylactic treatment of tuberculosis. As a result, our knowledge of the drug's actions and side effects is considerable. Among the various effects, the effects on the nervous system are of prime importance and are most frequent.

The aviation environment demands a level of performance that is seldom required elsewhere. Consequently, subclinical problems and side effects of INH or any other drug may cause difficulty in the aviator which would not be manifest in the general population. This leads to the conclusion that current knowledge of drugs should not be applied without reservation to aviators and that drug effects in this unique environment should be intensively studied.

An opportunity to pursue this objective arose at Fort Rucker. Several civilian instructor pilots were exposed to a case of active pulmonary tuberculosis. Subsequent tuberculin skin tests revealed a positive reaction in each case. In accordance with accepted medical standards, they were put on a program of INH therapy which was to last for one year. Many volunteered to participate in a study of the effects of this program on their flying performance. Neurological, general medical, psychomotor and ophthalmologic studies were done. The results of these studies are reported elsewhere.[37 38 86] The study by Shub, et. al.,[26] merely summarized the neurological results. The purpose of this paper is to present these in more detail. Computational errors which were discovered after publication of the first paper and a difference in the [illegible] subject population on which incidence figures are based will result in some discrepancies.

METHOD

[illegible] subjects were 58 civilian instructor pilots who volunteered to participate in the study. Twenty-one (21) subjects completed the entire 12 months of therapy (12-month subjects). Seven (7) subjects completed only [illegible] months of therapy (6-month subjects). The data presented in this paper are from the resulting 28 subjects. The data presented are principally that from the 12-month subjects. When data from the 6-month subjects are presented, they will be specifically noted.

The mean age of the 28 subjects was 47.2 years (range 39-57). The median age was 48 years. The mean ages of the 12- and 6-month subjects were 48.1 years and 44.4 years respectively.

To be included in this study subjects had to be in reasonably good health, free of tuberculosis and show a positive reaction to intradermal intermediate strength ppd (10 mm of induration after 48 to 72 hours). For additional details see Shub, et. al.[86]

There was no non-drug control group included in the study.

Experimental Design - The design of the study was that subjects were evaluated three times during the course of therapy: Once before taking INH (referred to as control or baseline), once 6 months after being on the drug (6-month exam) and once 12 months after being on the drug (12-month exam). The INH therapy consisted of a 300 mg daily oral dose (3-5 mg/kg body weight). Ten subjects also took or were given Vitamin B6 (pyridoxine-100 mg/day) for various reasons.

The design of the study was that each of the following measures would be taken at each examination period: Neurological history, clinical neurological examination, mental status examination, clinical electroencephalographic examination (EEG) and visual evoked potential (VEP).

Because of the complex nature of the methods and procedures employed in each of these examinations, the paper is organized into four separate studies.

LITERATURE REVIEW

A considerable amount of literature exists describing the various neurological side effects of INH. For clarity these are presented in summary form in Table 1 where the effects are lumped into nine (9) major categories. It will be noted that this categorization is not entirely adequate in that many of the entries might be classified in several ways and considerable overlap is unavoidable. The appropriate references are indicated. This list is not exhaustive; perhaps 50% of the existing literature is cited. The authors are not aware, however, of any other neurological complications not included in the table or discussed below. Some effects are not strictly neurological but included because of their interest to neurologists.

Various dosage levels and species have been employed in the studies cited. For completeness, all the effects are listed, but special attention

is given to the effects found in humans taking an amount of INH similar to this study and to effects found only with INH overdose.

Since its introduction in 1951 as a chemotherapeutic agent for tuberculosis, INH has been extensively used and studied. After an oral dose, peak serum levels are noted at 30 minutes[70 76] to one hour.[35 48] At five hours the level is 66% of peak[76] and at six hours it is 50% of the peak level.[32] The reported time required for complete serum clearance varies among authors. Twelve (12) hours,[35] 16 hours,[76] 24 hours[70] and over 24 hours[48] are reported. Elimination is via the renal route[35 48 95] and commences ten minutes after oral administration.[48] No accumulation of the drug in the human body occurs,[76 48] although Barlow, et. al., report accumulation in the cat hippocampus.[6] It is also reported that no protein binding occurs in the serum.[35] Peak excretion rates are noted from two to four hours after oral dosing.[70]

INH is excreted unchanged as the acetyl derivative. The respective percentages of secretion in each state are 4 to 32% and 5 to 65%.[70] There is a direct correlation of serum INH with free urine INH and an inverse correlation with acetyl-INH.[35 41] An interesting aberration of INH metabolism has been noted in mongolism. Compared to matched controls, mongoloids have been noted to have lower serum levels following the same oral dose. Their urine contained a lower than expected percentage of acetyl-INH.[100]

No localization of INH in the body is seen. There is equal distribution between the blood, brain, cerebospinal fluid and the visceral organs.[84 48]

It is well known that the population displays two patterns of metabolism with a less-well-defined group between the extremes, characterized as slow, intermediate and fast inactivators.[32] This distinction is made on the plasma INH level measurable six hours after an oral test dose. Six-tenths micrograms per ml seems to be the acceptable dividing point. Subjects with levels under 0.6 are classified as fast; over 0.6 as slow; and about 0.6 as intermediate.[19 35] It has been demonstrated that this difference results from varying genetic constitution. Fast inactivation is considered as an autosomal dominant and slow inactivation as an autosomal recessive trait.[24 35 84] A slim majority of the population can be expected to be slow inactivators,[11] and only 7% intermediate.[35] Slow inactivators have a greater percentage of INH in the unacetylated state[84] and, as expected, have more side effects from the drug (see below).

At the dosage levels employed in the present study most authors report few or no side effects. Most rates of side effects reported are in the range of .2% to 1%.[4 7 32] However, rates as high as 12% are reported.

At dosage levels of 10 mg/kg a 15% incidence is noted;[32] if 16 to 20 mg/kg, 22.5%;[7] and if 12 mg/kg, 51%.[75]

The reason for this discrepancy is unclear. One factor certainly must be the severity of the symptoms. One author might consider a mild symptom worthy of note; another might not. For example, the American Trudeau Society notes an overall incidence of 5%, but only 1% were serious enough that discontinuance of the drug was considered to be advisable.[95] Another likely factor is the means of diagnosis. Hanson, et. al.,[34] report 6.2% overall incidence of side effects, but base this figure on subjective reports. The hazards of this are illustrated by Ferebee[26] who found a 1.9% overall incidence but also an incidence of 1.5% with a placebo. True side effects occurred earlier. Other authors have noted as well that side effects are more common in unstable people.[101]

Ferebee[26] and Vysniauskas and Brueckner[101] report greater side effects with increasing age. This would not be unexpected since it is known that older individuals tend to have more drug-induced side effects.

Most symptoms take one and one-half to three months to develop.[26 101] One author reports a 12% incidence in his population six weeks after being on a dose of 20 mg/kg.[75] This increased to 51% at 20 weeks. The corresponding incindencse when vitamin B6 was added were 10% to 25% respectively. Toxic reactions are more frequent with concomitant alcohol ingestion[13] and less frequent with concomitant phenobarbital.[101] These factors as well as the dosage and type of inactivation need to be considered in evaluating any studies of the incidence of side effects. More studies such as the monumental PHS trials using large populations with matched controls would be quite desirable.[26]

Although nearly all studies report only mild complications with 3-5 mg/kg dose of INH, Vysniauskas and Brueckner[101] report severe side effects at this level. Therefore, it cannot be assumed that the drug is really as innocuous as claimed.

Side effects related to the nervous system [illegible] occur most frequently.[2 95] Thirteen and six-tenths percent of the reactions to INH noted in one study were neurologic.[7] Eight percent of the INH reactions are related to the CNS.[101]

The incidence of neurological involvement to be expected in any series of cases is comparable to the incidence of all side effects. Workers employing a 3-5 mg/kg dose find no neurological problems,[illegible] 0.5%,[illegible] 2.2%[34] and 3-4%[8] incidence. Ferebee[26] found that the percentage of complaints which were neurological was 16.8%. However, in a placebo group, the incidence was 7%.

At higher doses the incidence increases. With 6 10 mg/kg 8%,[8] 8-19%,[19] 0%[25] are reported. With 11-15 mg/kg 18%,[8] 33%,[17] 0%[55] With 16 to 25 mg/kg, 44%,[8] 37%,[75] 17%,[74] 29%.[50] Many of these figures are not specifically mentioned by the authors involved but extracted from their data as accurately as possible. The reasons for the discrepancies would include those discussed above. In addition, the previous drug history seems to play an important part. The incidence increases if INH had been taken previously.[8] Another factor is the way in which the drug is administered. Dividing the doses results in lower neurologic side effects,[19] presumably an indication that the peak levels achieved in the serum have etiologic significance.

Money[58] reported a 20% incidence in his subjects taking 4 to 6 mg/kg but most were alcoholics and undernourished--factors which many agree have bearing on the problem.

In nearly all the studies cited peripheral neuropathy was far and away the most common finding. Hyperreflexia, twitching, restlessness[75] and dizziness[41] are also mentioned as being common. The incidence increases with the time the drug is taken as in the incidence of general side effects Side effects are generally noted within four months.[41 75]

Little doubt exists at the present time that one or more of the analogs of vitamin B6 is intimately related to the neurological side effects of INH Many authors report that B6 either prevents or decreases the incidence and severity of neuropathy.[9 19 42 50 75 16 2 8] This phenomenon is seen even if as much as 20 mg/kg of INH is given.[9 75] An INH dose of this level almost invariably produces neuropathy. The vitamin appears to be more effective as a prophylactic agent than a therapeutic one.[9] Nearly all other neurological problems related to INH are reported to show alleviation with B6.[3 1] The question of whether B6 is effective in seizures is less clear. Some authors report no effect and feel that the vitamin has only peripheral effects and no effect on seizures or other CNS problems.[2 71] Others report the opposite.[71 50 32 57] It is even reported that B6 aggravates seizures caused by INH.[18 63 56] A correlation between the serum B6 levels in seizures and the presence of neuropathy has been shown.[50] In addition, a effect of B6 on seizures would be expected for another reason. "Pyridoxine dependency" which occurs in early childhood is rare but a well organized clinical entity where dramatic reversal of clinical seizures and cessation of EEG correlates thereof is seen with B6 administration This has been neatly accounted for by demonstration of the fact that B6 is a necessary co-enzyme for the synthesis of GABA, a presumed inhibitor transmitter. INH has been shown to decrease brain GABA,[77] although this effect is transient and GABA is increased later.[105] A therapeutic trial of this compound or glutamic acid has not been done, but would be of interest.

Why should this relationship of INH and B6 exist? The answer appears to be that a B6 deficiency is produced by INH. The mechanism of this interaction has been studied extensively Accelerated renal excretion of B6

is reported.[9 55 39] Direct metabolic antagonism has been shown,[14 39 75] including depletion of tissue vitamin.[14] Presumably this results from the structural similarity of the two molecules resulting in analog formation.[48] Pyridoxal and pyridoxal phosphate assist penetration of the blood brain barrier by INH.[18 63] It appears that this action accounts in part for some of the side effects seen and for the beneficial effects of supplemental B6 given with INH. An additional observation amplifying this point is the fact that conditions where subclinical B6 deficiency would be anticipated also show a higher incidence of side effects, such as malnutrition,[58] alcoholism,[58 10] old age[101 26] and debilitating disease, specifically TB.[9] Also, the neuropathy of INH is stated to be similar to the neuropathy produced by a B6 antagonist.[9]

In spite of the evidence, this suggestion is doubted by some,[39] because other signs of B6 deficiency are not seen with INH administration, such as glossitis and skin lesions. These have been reported with INH, however, even on low doses of 30 mg/day.[19 20 89 92] It is also suggested by some that the dietary deficiency is different than that produced by INH. The biochemical reactions, for example, are different.[43] One other possibility has been suggested. Cavenaugh[14] notes that clinically, the neuropathy of B6 deficiency and porphyria are similar, and that B6 deficiency has been shown in porphyria. He suggests that possibly the metabolic defect in porphyria and INH side effects is the same. INH has been shown to interfere with porphyrin metabolism.[33]

Other metabolic interactions of INH with other drugs have been noted. It has been observed that patients taking both INH and diphenylhydantoin develop toxicity whereas on an identical dose of diphenylhydantoin alone, they do not.[11 26 21] This phenomenon is seen more often in slow inactivators.[11 52] Fast inactivators had a steep rise of diphenylhydantoin plasma levels up to 7 days, which plateaued thereafter. In slow inactivators the initial rise was steeper and the plateau at a higher level. Those in the latter group who developed diphenylhydantoin toxicity showed a continuous rise of diphenylhydantoin levels with no plateau and the slope of the increase was far steeper than the other two groups. In all cases the diphenylhydantoin level was higher at all times than when no INH was given.

In cats with various dosages of INH, a direct correlation has been shown between the amount of INH given and the blood level of diphenylhydantoin. In vitro studies demonstrate that the mechanism of this effect appears to be non-competitive reversible inhibition of the enzyme system metabolizing diphenylhydantoin by parahydroxylation.[21 52] Inhibition was complete with 137 micrograms/ml of INH and 18% with 5 micrograms/ml.

Para-aminosalicyclic acid is frequently given with INH. It has been shown that this results in prolongation of the half life and flattening of

the peak levels of INH.[98] Ceruloplasmin oxidase is inhibited by INH, resulting in decreased degradation of serontonin.[31] Plasma, but not platelet monoamine oxidase, is also inhibited.[72] A possible synergistic effect with disulfiram exists.[102] Another interaction which may explain some effects is that INH inhibits intestinal transport of amino acids.[60 15]

Peripheral neuropathy is generally considered to be the most common neurological side effect of INH. As seen, it usually responds to administration of vitamin B6. Vitamin preparations containing all the vitamins except B6 have no effect but, interestingly, glutamic acid does appear to render preventive effects.[17] The incidence and severity is dose related,[16 32 7 75] increased in slow inactivators[32 33 50 16] and correlated with the serum INH levels.[19] Symptoms regress when INH is stopped,[2 8] although prompt and complete regression is observed only if no findings on the neurological exam are noted. The time of onset of symptoms is also dose related; higher doses cause earlier symptoms,[8] dividing the doses may delay the onset,[19] and the incidence is greater if the patient has taken INH earlier.[8] It is reported that the incidence of neuropathy is increased[8 19] and decreased[32] in individuals whose urine contains more free INH and less acetylated INH. One interesting report[50] describes decreased SGOT levels in patients developing neuropathy on high doses of INH with return to normal upon clinical clearing of symptoms by discontinuance of the drug or B6 administration.

By the time a patient has been on INH for ten months, it would be expected that symptoms or signs of neuropathy would be noted if they are going to appear at all,[19 8 9 30] although the delay may be in terms of years.[30] Initial symptoms are sensory-burning, numbness, paresthesia, etc.[30 8 14 88]

Only one study could be found which measures nerve conduction time.[88] This is regrettable since it is recognized that suggestibility and other non-neurological factors are important.[8 26] Yet, a decreased conduction time was seen. Cavenaugh[14] suggests that motor involvement occurs but is compensated early by regeneration and collateral sprouting of nerve fibers at the muscle level. This has indeed been demonstrated to occur in experimental animals on INH.[36] This might be reflected in physiologic measurements. More studies with careful control of stimulus parameters are necessary to settle the issue.

Symptoms begin distally and more proximal involvement is seen later.[30 1] Devadalta, et. al.,[19] studied patients taking 7.8 to 9.6 mg/kg/day of INH. Spontaneous complaints appeared after 2 to 10 months. Subjects were examined if complaints continued and were followed. Distal parestnesias were initially seen primarily in the feet. Distal weakness was noted by their patients but only in the hands even though all extremities appeared to be involved on examination. Other physical signs were largely limited to the

lower part of the body and consisted of hyperesthesia, hypalgesia, posterior column findings and loss of deep tendon reflexes. One patient had anesthesia of the right face, shoulder and scapular area. Initial signs were loss of vibration and ankle jerks followed by hypesthesia and loss of position sense. The severest cases had loss of ankle jerks and weakness. A slow progression and spread of findings were noted.

Biehl and Nimetz,[8] in investigating peripheral neuropathy, noted an early and late stage of development. The early stage consisted of only sensory symtpoms and were reversible. The late stages were seen only in subjects receiving 20 mg/kg and consisted of subjective and objective findings. Discontinuance of INH in these subjects produced some regression but abnormalities persisted for months. One year afterward some subjects still complained of burning, had atrophy, fasiculations and weakness, implying structural nerve damage. Some of their subjects developed contractures, but they felt this could not be definitely attributed to INH.

Seizures, when seen, are usually found in known epileptics or are more frequent in these patients.[95 48] It is rare to find a case in patients taking 300 mg/day. Yet cases of status epilepticus have been reported at these levels.[101 27] These have been, again, in previous epileptics.

In view of the metabolic interactions of INH and diphenylhydantoin, it is quite surprising that diphenylhydantoin is almost universally found to be ineffective in control of seizures induced by INH ([71] and below). Phenobarbital has been recommended,[71 101] but usually is only slightly better than diphenylhydantoin (see below). The effectiveness of B6 has been discussed, and in general is superior to conventional anticonvulsants. Pyruvic acid is stated to have a protective effect against seizures.[39] Dizaepam and depressant drugs have been employed with some successs ([70 71] and below). Susceptibility to seizures increases with steroids.[59]

Reilly, et. al.,[71] performed a carefully controlled study where the seizures producing effect of INH was quantified. It was noted that subjects who were taking INH experienced a lowered threshold for seizures produced by photic and auditory stimuli. The subjects all progressed through a characteristic photogenic seizure pattern starting with facial seizures. In doses ranging from 20 to 45 mg/kg only 35% of the trials produced seizures. Even 45 mg/kg did not always cause seizures. The authors concluded that a reliable convulsant dose could not be found within their dose range. Enhancement of photo-sensitivity is also noted in epileptic baboons with 50-150 mg/kg.[56]

The above results are quite surprising in view of the rest of the literature. The authors consider careful study of reports of INH toxicity from

overdose to be particularly instructive. The pertinent facts in several cases in the literature are summarized in Table 2. It will be noted that seizures are a feature of all cases. Assuming an average weight of 70 kg for the subjects in the study reported by Reilly, the dose of INH used would be over 3 gm. This dose produced status and death in one case.

Table 2 is not intended to be exhaustive--merely representative. Terman and Titelbaum[94] present an excellent literature review on this subject. Wherever known, the dose of INH is presented in mg/kg.

Several interesting features of this summary are apparent. First is the striking clinical similarity of toxic manifestations although a widely diverse group of patients is presented.

Coma and intractable seizures are seen in nearly all cases. Other similarities as discussed by Terman and Titelbaum include respiratory distress, metabolic acidosis, hyperglycemia and acetonuria. The acidosis seen in several cases is remarkable and often severe. Lactic acidosis is reported in conventional doses as well.[61]

Another feature is the notable lack of effect of the usual anticonvulsants to control the seizures, although diazepam is occasionally effective. Often the acidosis is responsible for this and correction of it results in control. It is not felt, however, that the acidosis per se causes seizures.[94] It seems that B6 is occasionally effective, sometimes dramatically so.[45] This may relate to the dose of B6 employed. It continues to be recommended, in cases of ingestion of more than 10 gm[29] and on a gram for gram basis with INH.[56] Another interesting point is that the interval between ingestion and seizures, when given, corresponds quite closely to the time when peak levels are noted on metabolic studies. Perhaps, as suggested, the rapidity of change of serum levels and resulting penetration of the blood-brain barrier is the basic pathogenesis involved.[94] The range of dosages involved reveals a wide individual tolerance. The case of death following 3 gm[85] is the lowest lethal dose of which the authors are aware. Perhaps the alcohol history contributed, in concert with earlier observations in this paper. However, the opposite appears to be true when alcohol ingestion was present in patients ingesting extremely massive doses with recovery.

It is stated that acute toxicity occurs after ingestion of 80 to 100 mg/kg,[23] and that certain death occurs with ingestion of 200 mg/kg.[12] Inspection of Table 2 will reveal that the last statement is untrue. More than twice that amount has been taken with favorable outcome. More than 8 grams has been consumed with absolutely no CNS effects.[62]

The cases reported by Nelson[62] in Navajo Indians are especially interesting because of the rapid recovery following sizable doses. However, all the children vomited some time after taking the drug, and they may have

absorbed only a small amount. Another unique feature is that the dose was carefully counted before ingestion and, therefore, quite reliable. The largest dose ever taken, to the author's knowledge,[1] was 40 gm, cited by Terman and Titelbaum.[94] The details were not presented.

Large doses in animals produce much the same picture with a good correlation between the plasma level and the toxic effects.[71 76] The animals appear to be more susceptible to INH than humans. One hundred fifty (150) mg/kg[71] or 9-35 microgram/ml[76] caused death. Transient CNS stimulation occurred with 6 to 8 microgram/ml.

In regard to the mental effects of INH, much less literature is available. A Scandanavian group[64 99] has done the greatest amount of work. Impairment of memory was noted in a majority of subjects taking conventional doses of INH. This effect was more prominent with higher doses. It was only partially reversible. Further investigation revealed this effect to be a combination of confusion and a subtle inability to concentrate on more than one task at a time, revealed by a test of their own design. Some of the psychophysiological measures in our Fort Rucker study were designed to specifically investigate this point.[37 38] In contrast to this report, no change in mental function[37 38] or a suggestive improvement have been noted.[26 97]

The issue of mood and personality changes is likewise controversial. Mood changes are said to be the earliest sign of toxic encephalopathy.[1] It is often noted that INH-caused psychosis is related to a previous unstable personality,[101 95] but not strictly limited to this.[101] It is often severe enough to require hospitalization.[15]

Some of the literature on experimental INH pathology in animals will be summarized in relation to the clinical problems discussed above. These studies were done on rats, mice, and ducks who were given INH in doses ranging from 125-360 mg/kg in rodents and 1000 to 1500 mg/kg in ducks.[15 36 54 65 49 91 107 67 81 83 5]

In studies concerned with the peripheral nervous system, with only one exception,[65] clinical changes were noted after pathologic changes had occurred or were not noted (presumably because the experiment was terminated before they would be expected). The delay was as long as 7 to 8 months in one case.[107] Severe pathologic changes were frequently seen, yet the animal was clinically normal[36] or only minimally involved.[15 65]

In contrast, early changes occur in the electromyogram and nerve conduction time. Hildebrand, et. al.,[36] studied rats given 330-360 mg/kg. An early slowing in nerve conduction time was seen; at first only sensory.

This was correlated with diffuse myelin disruption in 10% of the nerve fibers. When 32% of the fibers showed myelin changes and axonal fragmentation, motor end plate denervation and collateral sprouting and uniform atrophy of muscle fibers to 30% of normal size were seen. There was a decrease in muscle action potential, but the motor nerve conduction time showed only an increased dispersion of conduction. Only when 76% of the nerve fibers were damaged were both the sensory and motor conductions decreased. A myasthenic decremental response was seen occasionally. Continued administration of high doses caused no further damage but increased collateral sprouting was seen. At this stage no electrical abnormalities were noted. At no time were any clinical findings seen.

In other studies[65 15 91] the initial pathology is in the axon rather than the myelin. All fiber sizes are affected with the small and medium-sized being most affected.[15] This includes autonomic system.[91] Myelinated fibers are affected most.[81]

The motor system shows more involvement than the sensory system,[15] although the sensory axon changes occur sooner.[36] Although distal involvement is greater than proximal, early changes are found at both levels. Changes are generally described in the somatic system, but Smith[91] found only changes in the myenteric plexus. Smith also describes proximal changes occurring prior to distal changes.

The pathology found includes Wallerian degeneration, swelling, fragmentation, change of the internodal length, atrophy, folding and loss of organelles. In the myelin sheath demyelination, fragmentation, thickening, proliferation of granular endoplasmic reticulum and irregular or round Schwann cells are seen. Schroeder[82] found red blood cell accumulation and electrodense organelles in the histocytes of the endoneurium. He feels, therefore, that the degeneration of the axon is more than simple Wallerian. Amore's and Bonavita's results[5] would support this. They found only one out of several early biochemical changes (transient increase of LDH_5) that would be expected in Wallerian degeneration in their rats on INH. Pathology in the spinal cord appears to be secondary to nerve fiber lesions.[15 83] Also, at the neuromuscular junction the changes appear to be due to distal degeneration and regeneration.[36 15] Both the motor[17] and sensory[83] nerves of the muscle spindles show the same degenerative phenomena.

A species difference appears to be important. In rats and mice, peripheral pathology is described and central lesions are said not to occur.[15] In ducks central pathology is seen with no peripheral involvement.[49 54] The greatest involvement in ducks is in the white matter of the cerebellum involving all structures there with corresponding clinical signs.[49 54] The primary changes appear to be in the glial cells. In addition, ependymal cells, cerebellar cortex and nuclei, peduncles and the medullary reticular

formation are involved. In rabbits, decreased detectable neurotransmitter and neurone degeneration is seen in the hypothalamus, mostly in the paraventricular nucleus.[67] A material not further characterized was also seen in the pituitary.

Pathologic studies in the human nervous system are almost non-existent. Perivascular hemorrhages, optic tract demylinations, softening of the grey matter,[32] cerebral edema and degeneration[103] were noted in patients who died from an overdose of INH.

Simmons and Ambler[88] conducted the one study which most closely approximates the present study. Fifteen (15) healthy aviators, age not specified, were given baseline exams including EEG, median nerve motor conduction time, physical exam and INH blood levels. Following this 300 mg of INH were given orally in one morning dose and subjects were reexamined twice a week for the first two weeks and once a month thereafter. Subjects were studied for one year. No serious side effects necessitating removal from flying duties were encountered. All subjects were found to be rapid inactivators. Nerve conduction times were done on 13 of the subjects, but repeated on only three in the third month. Of these three, one showed a change from 82.5 to 53.3 meter/sec; one from 67.5 to 61.25 and 60 meter/sec; and one from 70.5 to 88.5 meter/sec. Both the subjects with the large decrease and the one with the increase in conduction time complained of paresthesias with the first reporting headaches as well. These complaints disappeared when INH was stopped. No other neurological complaints are noted. The EEG results are not mentioned.

The literature on EEG changes of INH is quite sparse. Few studies include the EEG as a parameter. No specific change appears other than one report of increased amplitude of occipital alpha and frontal spiking.[32] Triphasic waves were seen, but the patient also had cirrhosis.[51] A photomyoclonic or photoconvulsive response has already been noted.[28 71] A lowered threshold here is the only effect that might be attributed to INH.

Other findings are those expected in seizures from any cause and occurred in subjects experiencing seizures. They include paroxysmal slowing,[57 80 84] six and 14 positive spikes,[70] uncharacterized patterns consistent with seizures.[62] Temporal theta[70 84] and a temporal focus (of spikes?)[62] are noted but may result from anoxia due to the seizures rather than INH. Sharp theta preceding paroxysmal discharges described in this group as part of an allergic reaction may have a different significance.[54]

Even less literature exists on visual evoked potential changes. A decrease in threshold or response to auditory and visual stimuli has been noted previously.[71 72] This is also seen in b6 deficiency.[3] A change in the evoked potential would be expected, but this point has not been

studied. To the author's knowledge, no study of the evoked potential in INH exists.

A few additional interesting reports are worthy of note. In rats given enough INH to result in peripheral neuropathy a decremental response is seen on the electromyogram.[60] This implies decreased myoneural transmission and needs to be considered in the workup of myasthemia gravis. Spasticity, although a rare complication, may be a presenting feature of INH side effects.

In addition to the side effects, an allergic reaction has been reported with INH. Burning and flushing are a feature of this.[84]

Finally, clinicians need to recall that many of the phenomena of INH may be duplicated by the disease for which it is given, tuberculosis. An excellent review of some of the more unusual presenting features of TB are presented by Kocen and Parsons.[47]

TABLE 1

REPORTED SIDE EFFECTS OF INH

I. PERIPHERAL NEUROPATHY

**Paresthesia[8 9 19 26 30 31 88 69]
**Numbness[8 9 19 26 30 69]
**Burning[8 9 19 30 89 69]
**Weakness[8 9 19 30 68 69 1]
**Leg Pain[89]
**Calf Tenderness[8 19 89]
**Decrease Nerve Conduction Time[88 69]
**"Peripheral Neuropathy"[50 66 90 93 95 75]
Stiffness[8]
Hypalgesia[8 19]
Deep Tenderness[8]
Decreased Vibration Sense Distally[8 19 30]
Atrophy[8]
Fasiculations[8]
Prickling Pain[19]
Hyporeflexia[8]
Decreased Position Sense[19]
Hypesthesia[8 19 30]

II. CRANIAL NEUROPATHY

**Optic Neuritis & Optic Atrophy[2 42 69 32]
*Decreased Corneal Reflex[13]
*Dilated Pupils[13 70 94]
*Constructed Pupils[44]
*Decreased Pupillary Light Reflex[23 13 80 44]
**Iridoplegia[2]
**Cycloplegia[2]
*Blurring of Disc[69 32 64]
Burning in Face[19]

III. AUTONOMIC DISORDERS

Postural Hypotension[48]
**Flushing[19 96]

*Reported with overdose only
**Dose of 5 mg/kg/day or less in humans

TABLE 1

REPORTED SIDE EFFECTS OF INH (Continued)

Dryness of Mouth[88 73]
*Salivation[76]
Syncope[95]
**Difficulty with Urination[95 96]
Tachycardia[75]
*Irregular Pulse[76]
*"Stimulation"[44]
Bradycardia[69 33]
Sweating[19]

IV. VESTIBULO CEREBELLAR DISORDERS

**Vertigo[26 34 44 32 48 33 73]
**Giddiness[66]
**Dizziness[26 34 42 75 48 96]
Ataxia[49 75 76 44 69 32 33]
*Intention Tremor[49 48]
Tinnitis[44 32]
Dysarthria[10]
Decreased Fine Coordination of Hands[19]
*Nystagmus[80]

V. CNS STIMULATION

**Hyperreflexia[8 80 48 73 1 95 96]
**Clonus[80 1]
**Seizures[1 23 42 46 50 51 13 62 68 70 71 75 76 77 79 80 90 94 101 44 32 48 33 57 73 29 45 1 95]
**Tremors[76 69 33 96]
Hyperventilation[94 69 33]
Respiratory Distress[94]
**Twitching[42 101 69 32 33 73 95 96]
**Insomnia[93 101 44 69 95]
Lower Sensory Threshold[71]
**Restlessness[80 94 101 69 95 96]
Excitability[76]
**Spasticity[1]
*Running Movement (Animals)[76]
**Nervous[101 95 96]
**Involuntary Movements[1]

TABLE 1

REPORTED SIDE EFFECTS OF INH (Continued)

VI. CNS DEPRESSION

Stupor[42 75 32]
**Lethargy[3 31 46 13 75 90 94 44 32 33 96]
*Coma[10 23 46 68 90 103 44 45]
*Respiratory Depression[13 76 90 44 69]
**Pyramidal Tract Signs[10 1]
*Hyporeflexia[13 70 94 44]
**Decreased Superficial Reflexes[1]
**Paraplegia[1]

VII. MENTAL CHANGES

**Confusion[10 75 85 101 69 32 99 1]
**Psychosis[42 51 75 101 69 32 95]
**Korsakoff Syndrome[1]
"Toxic Encephalopathy"[42 68 32]
**Disoriented for Time and Place[101]
Euphoria[42 32]
**Agitation[1]
Memory Disturbance[80 44 32 99]
**Delirium[1]
Separation of Ideas and Reality[32]
Loss of Self Control[3 32]
**Irritability[93 101 1 96]
**Depression[101 69 32 106]
"Unbalanced State of Mind"[106]
**Apathy[1]
*Illusion[44]
**Hallucinations[101]
*Delusion[44]
**Irrational[101]
**Incoherent[101]
**Uncooperative[101]
Personality Change[69]
**Emotional Lability[31 101]
Decreased IQ[32]
Apprehension[19 95]
**Argumentative[101]
Premonition of Death[19]
**Paranoid Ideation[101 1]

TABLE 1

REPORTED SIDE EFFECTS OF INH (Continued)

VIII. NEUROMUSCULAR

- Weakness
- Muscle Tenderness
- Myasthenic Response[60 36]
- Contracture[8 31]

IX. OTHER

- **Headache[26 88 101 44 33 95]
- *Exhaustion[80]
- *Gagging[80]
- "Visual Disturbances"[89]
- Flame Hemorrhages - Fund...[2]
- **Night Walking[96]
- Collagen Vascular Disease Syndrome[22 31 40 78 87]
- Increase in Amount of Dreaming[101]
- **Visual Acuity Decrease[2 1]
- Worsened Conditioned Reflex[28]
- Neuromyelitis Optica[21]
- Myelopathy[58]

TABLE 2

SUMMARY OF SELECTED CASE HISTORIES WITH AN OVERDOSE OF INH

Ref	Subject	Dose of INH	Neurological Symptoms	Neurological Findings	Treatment	Outcome
12	2	313 mg/kg 204 mg/kg	Seizures	Papilledema Neuropathy	Barbituates Dialysis Vitamin B6	Full Recovery
23	32 month	2100 mg	Seizures Coma	Decreased pupil light reflex Babinski	Barbituates Vitamin B6*	Recovery
	2½ yr.	?	Seizures Coma	Decreased pupil light reflex Hyperreflexia	Barbituates Vitamin B6*	Recovery
46	15 yr.	5 gm	Seizures Coma		Barbituates Vitamin B6* Dialysis	Death in 70 hrs.
13	42 yr. Alcoholic	240 mg/kg	Status Epilepticus Coma	Fixed dilated pupils Decreased corneal reflex	Barbituates Vitamin B6 Steroids	Recovery
62	15 yr.	6 to 7 gm	Headache Seizures 1 hr later		Sedatives	Recovery in 24 hrs.
	15 yr.	5.9 gm	Seizures 1 hr later		"Symptomatic"	Recovery in 24 hrs.
	15 yr.	6.4 gm	Seizures 1 hr later		"Symptomatic"	Recovery in 24 hrs.

*Effective in Seizure Control

TABLE 2 (Continued)

SUMMARY OF SELECTED CASE HISTORIES WITH AN OVERDOSE OF INH

Ref	Subject	Dose of INH	Neurological Symptoms	Neurological Findings	Treatment	Outcome
62	16 yr. 14 yr.	 1.5-2 gm	Headache Seizures Status 1½ hr later		"Symptomatic" Vitamin B6	Recovery in 24 hrs. Recovery in 48 hrs.
68	2 yr.	120 mg/kg	Seizures 1 hr later Coma	Weakness RT grip 24 days	Vitamin B6 Barbituates Thiamine	Slow recovery Late seizures
70	14 yr. 22 yr.	50 mg/kg 93 mg/kg	Seizures Headache Seizures 2 hrs later	Normal Dilated fixed pupils Areflexia	Supportive Valium* Dilantin Barbituates Vitamin B6	Recovery Recovery
80	17 yr. Inebriated	30 gm 461 mg/kg Serum - 511.5 mg/ml peak	Malaise, gagging Seizures Status Coma?	Nystagmus Hyperreflexia Decreased pupil light reflex } 3d Day Retrograde amnesia - 2 weeks	Barbituates Valium Dialysis	Recovery
85	40 yr. Alcoholic	3 gm	Confusion Status 4 hrs later Coma		Barbituates	Death in 7 hrs.

*Effective in Seizure Control

TABLE 2 (Continued)

SUMMARY OF SELECTED CASE HISTORIES WITH AN OVERDOSE OF INH

Ref	Subject	Dose of INH	Neurological Symptoms	Neurological Findings	Treatment	Outcome
90	37 yr.	20 gm Serum - 143 mg/ml	Seizures Coma	Transient neuropathy	Dialysis*	Recovery
61	20 yr.	20-30 gm	Delirious Seizure Coma	Nystagmus - 1 day	Barbituates Dilantin Valium Paraldehyde IV Bicarbonate Dialysis	Full recovery
94	35 yr. Alcohol ingest. Active TB	? 71 mg% (?!)	Seizures	Fixed dilated pupils	Barbituates Dilantin Vitamin B6 Paraldehyde Dialysis*	Recovery
	21 yr. Active TB	30 gm PAS also	Seizures 1 hr later Status Coma	Dilated pupil Hyporeflexia	Dialysis* Dilantin Barbituates	Recovery
	16 yr.	10 gm	Lethargy Restless Status		Dilantin Barbituates IV Bicarbonates* (Acidosis)	Recovery

*Effective in Seizure Control

TABLE 2 (Continued)

SUMMARY OF SELECTED CASE HISTORIES WITH AN OVERDOSE OF INH

Ref	Subject	Dose of INH	Neurological Symptoms	Neurological Findings	Treatment	Outcome
94	20 yr.	?	Hyperventilation Seizures Coma	Disc margin blurring	IV Bicarbonate Dilantin Barbituates Paraldehyde Valium* Dialysis	Recovery
44	18 month	?	Seizures Coma	Fixed constricted pupils Hyporeflexia Ataxia Spasticity? Lethargic } Later	Barbituates Vitamin B6 Dialysis	Recovery
45	22 cases	Up to 30 gm	Seizures Coma		Vitamin B6* Large doses	
29	18 yr.	30 gm	Seizures Coma		Anticonvulsants Vitamin B6 Dialysis	Death in 44 hrs.

*Effective in Seizure Control

STUDY 1

NEUROLOGICAL EXAMINATION AND CLINICAL NEUROLOGICAL EXAMINATION

PROCEDURE

History - Subjects were asked to complete a prepared questionnaire which contained questions relating to all the neurological side effects of INH. Subsequent interviews were held with each subject to define further any answer suggesting relevant symptomatology.

Neurological Examination - The neurological examination consisted of nine subtests as detailed below:

1. Autonomic Nervous System Function - Autonomic nervous system function was evaluated by measuring the resting vital signs after lying at least 30 seconds, the vital signs immediately after rapid assumption of the standing position and by inspection of the mucous membranes.

2. Reflexes - All the usual deep tendon reflexes and all four abdominal reflexes were elicited and graded on a scale of -4 to +4 (-4 = no response, 0 = normal and +4 = sustained clonus). The plantar response was recorded.

3. Sensory Nervous System Function - Pain and light touch sensibility were evaluated in all dermatomes. Vibration and proprioception were evaluated bilaterally at the level of the great toe.

4. Cranial Nerve Function - The function of all the cranial nerves except the first was tested including a fundoscopic examination.

5. Muscle Power - Distal muscle power was evaluated by testing the interosseous, toe dorsiflexor, flexor digitorum profundus and superficialis, pronation and suppination function bilaterally; proximal muscle power by forearm flexion and extension as described below. The results were graded on a scale of 0-100% (0% is no measurable contraction, 50% is just enough power to overcome the force of gravity and 100% is the full power an individual of comparable age would possess).

6. Functional Tests - Testing was accomplished by having subjects stand and hop first on one foot and then stand on the toes of that same foot. This was done for both the left and right foot. The time required to do 20 pushups and 20 deep knee bends was recorded. If the subjects were unable to do 20 pushups the number they could do was recorded. Finally,

the subject was required to lie supine and maintain all limbs at a 45° angle from the horizontal position. The limbs were not allowed to contact each other, and the knee and elbow joints had to be in full extension. The subject was timed from the onset to the point where any limb touched the examining table and this time recorded. Observation for muscle twitching was done at all times.

7. Cerebellar Function - Cerebellar function was evaluated by the finger to nose test, ability to make rapid alternating movements, the Rhomberg Test, observation for nystagmus and intention tremor and by observation of responses in the other tests which bear on cerebellar function.

8. Gait - The subjects were observed while ambulating normally with eyes open and eyes closed. Heel, toe and tandem walking was observed.

9. Handwriting - Subjects were asked to copy a few sentences from material which remained the same at each evaluation. This test was designed to assess handwriting and observational accuracy.

10. Peripheral Neuropathy - Evidence for the existence of peripheral neuropathy was derived from four areas: Decreased deep tendon reflexes, corresponding muscle weakness, corresponding sensory complaints and corresponding symptoms. Changes were required in two of these four areas before a subject was considered for a diagnosis.

DATA ANALYSIS

Each of the measures taken in this study was compared at 6 and 12 months, for each subject, to his pre-drug baseline measure in order to determine the presence or absence of a clinical change. In most cases a progressive increase or decrease was required.

When either the 6 or 12 month exam showed more clinically notable findings or when several measures at one examination period showed a pattern which, when considered together, suggests a valid clinical problem a change was recorded.

An attempt was made subjectively to assess the relationship ("subjective correlation") between various clinical measures, the Vitamin B6 administration, system involvement and the INH inactivation levels.

"Multiple system involvement" means that the subject showed a change in more than one subtest.

The INH inactivation levels were determined as part of the overall study done by Shub, et. al.[86] Each subject was classified as a rapid, slow or intermediate inactivator.

RESULTS

History - The subjective symptoms reported by the subjects in the questionnaire and in the subsequent interviews are summarized in Table 3. All symptoms reported are listed along with the number of subjects reporting the symptom, their mean age and the percentage of the total group represented. The last column shows the number of subjects with neurological findings related to the symptom. These are called associated findings. Associated means a symptom which would be expected to occur with a particular disease process and probably related to it. For example, paresthesias would be considered an associated symptom of peripheral neuropathy.

The mean age of the 17 subjects with symptoms was 46.7 compared to the mean age of the entire group which was 47.2. This difference was not statistically significant.

Inspection of the table reveals that the deviations of the mean age of the subjects reporting various symptoms from the mean age of the group are in the directions expected for the nature of the symptom. An exception to this was in the case of blurring of vision. It would be anticipated that older subjects would report more blurring but the data reveal that 14.3% of the subjects reported this symptom and had a mean age two years below the group mean.

Paresthesia was the most frequent symptom by far (28.6%). Almost 40% of the group with associated neurological findings were represented by the subjects with paresthesias.

Autonomic Nervous System Function - Definite orthostatic changes in vital signs occurred in two subjects. In one subject this change was seen only at the six month exam. The changes in the remaining subjects were within normal limits.

Reflexes - As mentioned previously reflexes were graded on a scale from -4 to +4. All subjects showed some variation in grading. For this reason a difference of ±3 from baseline had to be reached or maintained in accordance with the criteria outlined in the data analysis section.

Nineteen (19) subjects showed reflex changes in accordance with these criteria. Eighteen (18) showed decreases and one showed an increase. Two of the 19 subjects showed reflex changes only at the six month exam. All

TABLE 3

NEUROLOGICAL SYMPTOMS

	Symptom	No. of Subjects[1] With Symptom	Incidence (% of Total Group)	Mean Age	No. of Subjects With Associated Findings[4]
1.	Paresthesias[2]	8	28.6	48.6	4
2.	Cramps	1	3.6	(49)	0
3.	Burning	2	7.1	51	0
4.	Orthostatic Giddiness	1	3.6	(49)	1
5.	Weakness[3]	3	10.7	52	2
6.	Fatiguability	2	7.1	51	1
7.	Malaise	1	3.6	(52)	-
8.	Muscle Ache	1	3.6	(50)	1
9.	Nervousness	5	17.9	45.4	-
10.	Cloudy Thinking	1	3.6	(43)	1 (Mental Status)
11.	Decreased Visual Acuity	1	3.6	(46)	-
12.	Back Pain	2	7.1	46	-
13.	Tinnitus	2	7.1	51	1
14.	Blurring of Vision	4	14.3	46.5	-
15.	Insomnia	3	10.7	50	-
16.	Tremor	1	3.6	(52)	0
17.	Agitation	1	3.5	(44)	-

[1]Seventeen (17) out of the total of 28 subjects had symptomatic complaints.
[2]Items 1 to 3 are considered symptoms of neuropathy and matched with that diagnosis in column 5.
[3]Items 5 to 8 are considered symptoms of weakness and matched with that finding in column 5.
[4]Includes all neurological findings listed in Appendix 1.

these changes were marginal or "suggestive" and would not be considered significant in the usual clinical situation.

Three subjects showed reflex asymmetry, two in the abdominal and one in the brachioradialas and ankle jerk.

Sensory Nervous System Function - Two subjects showed hypesthesia. In one subject this was located in the anterior tibial area only and in the other it was located in the distal leg. No subjects showed decrease in light touch sensation. Eight subjects showed decrease in vibration sense and six showed decrease in proprioception.

Of the subjects that showed sensory changes, five had changes in more than one modality.

In all, 11 subjects showed changes in sensation. In three subjects the change was noted only at the six month exam, and in one only at the 12 month exam.

These findings were barely detectable and in and of themselves would not be considered as representative of clinical difficulty.

Cranial Nerve Function - No subject showed any detectable change in cranial nerve function on the clinical exam.

Eighth cranial nerve function was evaluated on all subjects by Shub, et. al.,[86] using audiograms and ice water calorics. Two subjects had tinnitus. The tinnitus in one subject showed marked progression and changes were noted on his audiogram and ice water calorics. For this reason, this subject was considered to have 8th nerve involvement. This was the only incident of any cranial nerve involvement noted.

Muscle Power - Seven subjects showed decrease in muscle strength. Of these, five were considered to be a possible clinical change; "possible" in that no subjects approached a level of weakness that would be indicative of clinical disease.

In the other two cases the scores were indicative of a change but were within the range of scoring error and, therefore, could be no more than normal variation. Since a doubt exists, these cases have been included.

The weakness noted was diffuse in five cases and localized to the arm in one case. One subject showed only proximal weakness.

In all cases except one, the weakness was persistent throughout the study.

Functional Tests - The role of the functional muscle tests was to provide additional information on muscle power. The results paralleled those found in the conventional muscle power tests.

Cerebellar Function - Eight subjects showed some findings on the cerebellar testing. The findings consisted of an unsteady Rhomberg in four, intention tremor in five, drifting of the arms in two and dysdiadochokinesia in one. One of the eight subjects had cerebellar findings only at the six month exam. One other subject showed an unsteady Rhomberg at the six month exam only, but had intention tremor at the six and 12 month exam.

Three of these eight subjects showed a magnitude of change great enough that a clinical impression of "possible" cerebellar dysfunction was drawn. In the remaining five subjects a "change" was noted which could easily have represented a variation of normal.

Nystagmus was seen in four subjects. In each case the nystagmus was more than just end point nystagmus. It was persistent in two subjects, present only at 12 months in one, and present only at six months in the other.

The nystagmus was horizontal in all cases except in the subject with nystagmus at six months only, where it was vertical and oblique.

The finding of nystagmus was considered a valid clinical change in all the cases except the subject with nystagmus at 12 months. In that case it was merely considered as suggestive and not worthy of further consideration due to the small magnitude of the finding and no time of appearance.

Gait - No abnormalities of gait were noted in any subject.

Handwriting - Analysis of the handwriting samples revealed no consistent change in accuracy of motor reproduction either individually or in the group as a whole.

A summary of the findings and symptoms of each subject will be found in Appendix 1. Table 4 includes only those changes which were considered to be "possible" changes and excludes those which were mentioned as changes within the range of normal variation, "suggestive" changes, "marginal" changes, changes within the range of scoring error or "change." The findings summarized in Table 4 are those which are indicated in Appendix 1 with a dark line.

The question still remained about the validity of dichotomizing these findings in this manner. An assumption was made that only a valid clinical

TABLE 4

NEUROLOGICAL FINDINGS
(16 Subjects Total)

Neurological Change	No. of Subjects	Incidence % Overall	Mean Age	Associated Symptoms No. Subjects	Percent
1. "Possible" Neuropathy	3	10.7	46.7	2	67
2. "Evidence" of Neuropathy	6	21.4	50.0	2	33
3. "Possible" + "Evidence"	9	32.1	48.9	4	44
4. Orthostatic Changes	2	7.1	46.5	1	50
5. Nystagmus	3	10.7	48.3	-	
6. Cerebellar	3	10.7	43.3	0	
7. Weakness	5	17.9	48.6	2	40
8. Reflex Asymmetry	3	10.7	46.3	-	
9. 8th Nerve	1	3.5	(50)	100	

change occurred it should be accompanied by associated symptoms. Therefore, the "possible" changes were compared to the more questionable changes in respect to associated symptoms. It was found that there were no associated symptoms with any "questionable" finding and that all the associated symptoms were in the group of subjects with "possible" findings. This finding lent some credence to the dichotomy of "changes."

Table 4 should not be construed as representing definite clinical changes, because the findings reported are of extremely small magnitude and might better be denoted as "subclinical" findings. No changes which would be expected to cause difficulty with occupational or daily activities were found.

Nine (9) subjects (32.1%) were found to have some evidence of peripheral neuropathy. In six of these cases (21.4%) this evidence was insufficient to make a diagnosis of anything other than "evidence for peripheral neuropathy." In the other three (10.7%) cases more evidence was present, but the magnitude of this evidence was still insufficient to make a firm clinical diagnosis. These cases are therefore referred to as "possible neuropathy," and are described below.

Subject 20: The subject had marked progression of vibration and proprioceptive loss, far more apparent than in other cases. He also developed deep tendon reflex asymmetry and an unsteady Rhomberg. Although there were no subjective complaints, the sensory progression was so compelling that a diagnosis of "possible neuropathy" was made.

Subject 26: Weakness and a decreased vibratory sense were seen on the neurological exam. Paresthesias developed quite early and were relieved by Vitamin B6. Primarily because of this history, the diagnosis was made.

Subject 13: Although a few physical findings were present, they appeared to be time-related to rather severe paresthesias which were completely reversed with B6. The diagnosis was made basically on the same grounds as it was for subject 26.

Unfortunately, neither subject 13 nor 26 was seen at the time of his greatest difficulty when a more positive diagnosis might have been possible.

As in the case of symptomatology an attempt was made to determine if the mean age of the subjects with the various types of findings differed from the group mean. The greatest difference found was that the group

with cerebellar findings was almost four years younger than the mean. Although this difference appeared significant, the small number of subjects precluded statistical testing.

The mean age of the subjects with "evidence" of neuropathy was almost three years above the group mean. However, this difference is not maintained in the case of subjects with "possible" neuropathy who are slightly younger than the group mean. Therefore, it appears that there is no consistent relationship between age and neuropathy.

The mean age of all the subjects with findings (those listed on Table 4) was 47.8 years, 0.6 years above the mean. This difference was not statistically significant.

Table 4 shows the number of subjects with associated and non-associated symptoms. Approximately 50% of the subjects in each category of neurological findings had associated symptoms.

Several subjects had involvement of more than one system (See Appendix 1). The data on multiple system involvement are summarized in Table 5. It might be expected that older subjects would show a greater tendency toward multiple system involvement. However, this did not seem to be the case considering the mean ages. There was a tendency for the mean age to increase from one- to two-system involvement. The failure to maintain this trend may be due to the small number of subjects with three systems involved.

The symptoms and signs are also noted on Table 5. Table 5 indicates that most subjects showed involvement of only one system. The total number of signs and symptoms was also greatest in the one-system group. The data do not indicate that involvement of multiple systems is accompanied by greater numbers of either signs or symptoms.

Although not detailed in the table, certain individual signs and symptoms were predominantly concentrated in one group. The two-system group had most of the paresthesias. Weakness, both subjective and objective, was also most prevalent in this group. All the orthostatic findings were in the one-system group.

Ten subjects (35.7%) took Vitamin B6. These subjects accounted for 38% of the neurological findings and 41% of the symptoms. The differences in percentage figures were insufficient to permit a conclusion that this group differred from the rest of the subject population. This assumes that symptoms and findings should be randomly distributed among the subjects.

TABLE 5

MULTIPLE SYSTEM INVOLVEMENT

	NO. OF SYSTEMS INVOLVED					
	1		2		3	
No. of Subjects	9	(56%)	5	(31%)	2	(13%)
Mean Age	45.4		51.4		45.5	
No. of Symptoms	10	(42%)	12	(50%)	2	(8%)
No. of Neurological Findings	10	(38%)	10	(38%)	6	(23%)
Total No. of Signs & Symptoms	36	(50%)	26	(37%)	9	(13%)
No. on Vitamin B6	2		4		0	

The assumption was applied to each individual sign and symptom since lumping them together may have obscured more specific effects. This means that one out of three subjects with any finding or symptom would be taking B6. This distribution was found in all cases except: None of the subjects with cerebellar findings, only one of the four subjects with blurring, none of the subjects with back pain and only one of the six subjects with "evidence" of neuropathy were taking B6.

Another way of looking at the effects of B6 is to see if there is any correlation between the administration of B6 and a change in a finding or symptom. This was found in three cases: Two of the three subjects with "possible" neuropathy and one subject with weakness. Improvement was reported in all three cases when B6 was taken.

The effect of B6 on multiple system involvement was examined. Table 5 shows that none of the subjects with three-system involvement were taking B6, but four of the five with two-system involvement were. The inconsistent nature of these findings and the small number of subjects involved preclude any definite conclusions.

Since INH inactivation patterns were unavailable in many cases, the data are insufficient to postulate any correlations between INH levels and clinical difficulties. However, a few findings of interest are noted. Twice as many of the symptomatic subjects with known INH inactivation patterns were slow inactivators as fast or intermediate; two of the three subjects with possible neuropathy were rapid inactivators. In the remaining measures, the number of subjects with rapid, slow and intermediate inactivation patterns were about equal.

The time of appearance of symptoms and signs was studied. The results are presented in Table 6. It will be noted that all the neurologic findings were seen by six months and three quarters were persistent and that nearly all the symptoms were noted by six months but most were not persistent. In both cases very little was noted at 12 months. Blurring of vision was the only symptom or sign which did not follow the general rule of appearing at six months. One subject of three with blurring experienced it at six months; two of the three experienced it initially at 12 months.

DISCUSSION

The most frequent symptoms was paresthesias which was reported by 29% of the subjects. The most frequent sign was peripheral neuropathy, found in 32% of the subjects. Other studies have also reported these as the most frequent sign and symptoms although the incidence figures reported in the present study are higher than generally reported.

TABLE 6

TIME AND APPEARANCE OF NEUROLOGICAL FINDINGS AND SYMPTOMS

	TIME NOTED		
	6 Mos. Only	6 & 12 Mos.	12 Mos. Only
Neurological Findings	3 (25%)	9 (75%)	0
Symptoms	17 (55%)	9 (29%)	5 (16%)

The literature indicates that when minimal changes are sought, incidence figures will increase. The reason for this is obvious. The clinical findings in this study were indeed minimal. Because of this it is possible that experimenter error was introduced which could account for some of the changes seen.

Very few studies in the literature indicate the amount of clinical change accepted as a valid change or the minuteness of the effort employed in examination. Consequently, it is impossible to compare directly the incidence figures in this study to other studies. Assuming that the present study employed greater scrutiny, the higher figures would be understandable.

A second possible reason why the incidence figures in this study are higher than those previously reported is that the subjects in this study were older. It is frequently pointed out in the literature that higher frequency of side effects is associated with older age.

A third possibility is the fact that the subject population in this study consisted solely of aviators. Part of the character traits of aviators might cause them to react differently to minor changes in their physiology (i.e., they may show more concern about their health). In addition, the demands of the aviation environment would be expected to accentuate minor clinical abnormalities.

On the other hand, Army flight surgeons know that aviators flying for the military are very reluctant to report medical problems for fear of being grounded. This is especially important in the case of our subjects whose livelihood is dependent on flying. This factor may have worked to bias the incidence figures in a conservative direction.

Another possible conservative bias operating in this study was the incompleteness of the examination. Certainly it cannot be said that it was complete, and it might better be termed a screening examination. The limited time allotted for examination of the subjects precluded the use of a more complete clinical assessment, but it was felt that the examination employed at least sampled the major areas of neurological involvement.

Since the literature indicates that older subjects would be expected to develop more clinical problems while taking INH, an attempt was made in this study to find correlation between age and various symptoms and signs. No obvious correlation was found. There were some trends noted in the expected direction. The negative correlation found between age and cerebellar finding and non-specific CNS symptoms was unexpected.

Any attempt to establish a definite relationship between age and these

measures in this study suffers from two limitations: Marked attenuation of the age range of the subjects and the small number of subjects at each age and in each clinical category.

The literature amply demonstrates an ameliorating effect of Vitamin B6 on the side effects of INH. Since the intent of this study was not investigation of relationship of B6 to INH, our subject should not have been allowed to take B6 without a clinical indication. However, as mentioned previously, 35% of the group were taking it and the administration was not closely controlled so that the dosage and total amount taken was not known in most cases.

Normally these subjects would be eliminated from the study. It was decided, however, to include them and attempt to study the effects of B6.

Study of the data revealed no clear differences between the group taking B6 and the remaining subjects. However, in three cases, the subjects reported an amelioration of symptoms related to B6. These were two cases of possible neuropathy and one case of weakness.

A proper design for study of this problem would have included a random selection of the group designated to take B6. This was not the case in this study. It is known that subjects who received B6 received it because of clinical symptomatology, although the nature of the complaint and the results of the B6 are not known. Taken together, these facts preclude any definitive statement about B6 effects in this study.

Correlation of INH inactivation patterns and other measures taken was also attempted. It is well known that individuals with slow inactivation patterns have more side effects. Confirmation of this fact was not obtained because of the marked incompleteness of the data collection. This situation resulted from the fact that the support laboratory stopped making INH determinations and from the fact that many of the known inactivation patterns were in subjects with no symptoms or signs.

Review of the literature revealed that many authors studied the clinical effects of INH in many ways, but none of the studies employed a data analysis technique based on the number of systems involved. It was hypothesized in the present study that multiple system involvement might be correlated with other clinical measures. This hypothesis did not receive any support from the data.

While there were nine subjects that showed signs and/or symptoms of peripheral neuropathy, it must be kept in mind that six of these had what could only be described as "evidence" of peripheral neuropathy. These cases are equivalent to findings in other systems considered as marginal

but are included with the data on possible changes because of the high interest of most readers in neuropathy related to INH.

The significance of the three cases of "possible" neuropathy and the six cases of "evidence" of neuropathy cannot be ascertained due to the lack of a suitable non-drug control group and the lack of data on the variations of the neurological findings over the course of a year.

The validity of classifying subjects as "possible" or "evidence" of neuropathy on the basis of marginal findings or symptoms primarily might be questioned. Previous studies have provided support for this procedure. The normal progression of disease is that subjects first have symptoms alone, then symptoms plus marginal findings, then symptoms plus definite findings.[8 14 30] Studies on INH have shown that by the time symptoms occur, structural damage is present. The study by Simmons and Ambler[88] supported this, since slowing of nerve conduction time was seen at this stage.

A nerve conduction time would have been the most helpful measure that could have been added to this study. Inclusion of these data would have permitted a much more positive diagnosis of neuropathy and permitted a correlation of the data from this study with the data from other studies. Although inclusion of this measure was strongly desired, the logistics of the overall study did not permit this.

In view of the above, it does not seem unwarranted to suggest that the diagnosis is justified in the three cases of "possible" neuropathy.

One subject had rather definite scapular paresthesias and part of the history suggested radiculopathy. A paucity of findings was present on physical exam. Devadalta, et. al.,[19] report a similar case. This raises the suggestion that scapular paresthesias may represent a more unusual and overlooked side effect of INH.

Nearly all the signs and symptoms were noted at the six month exam in good agreement with the literature. The fact that symptoms appeared to be largely transitory also agrees with the literature, but then the clinical findings should parallel the symptoms. The results of this study do not show this to be the case. No simple explanation is readily apparent.

The operation of any of several factors is possible. The clinical findings may have been overinterpreted at both the six and 12 month examination. The symptoms may have been spuriously elevated at six months or decreased at 12 months. It is also possible that the clinical findings represented pathology due to INH and that the subjects had adapted so that at 12 months they were less aware of their difficulties.

Blurring of vision appeared to be a unique symptom. It stood out from the other symptoms in its delayed development. While the data suggest that the latency of development of visual blurring may be prolonged over other symptoms, the number of subjects involved does not permit this conclusion. If all four of the subjects with blurring developed it at 12 months, perhaps more could be said.

Two subjects volunteered a history of alcoholism. While the side effects in these individuals were not particularly greater than the rest of the group, in contrast to what the literature would suggest, no conclusions regarding the interaction of alcohol and INH are justified from data with only two subjects involved.

This study was an "experiment of opportunity" and certain limitations and deficiencies in the experimental design were unavoidable. Several problem areas were encountered in analyzing the data. These have been alluded to previously and will be summarized here.

The lack of adequate control data was one of the principle obstacles in data interpretation. This resulted partially from the absence of a non-drug control group. Of greater importance perhaps is the fact that only one examination served as the baseline for all parameters. In order to adequately establish the true baseline plus the repeatability of the measures, more control exams should have been done. This is particularly applicable in the area of EEG and evoked potential where considerable variability is known to exist. For example, it is not possible to identify and label the individual deflections of the evoked potential with certainty without these repeated baseline measures. Only one baseline examination was obtainable due to the clinical indications for prompt initiation of therapy.

The second major problem area over which the authors had no control was the fact that no supervision of the administration of the INH was exercised. Subjects were merely given a supply of INH with instructions. In some cases the assurance that directions were followed was in question.

A third factor which could have been of some assistance in data interpretation would be follow-up data after the subjects discontinued INH. Most subjects were not available for further study.

SUMMARY

Several neurological signs and symptoms are reported in subjects taking INH in this study. Although the incidence figures are high in

some cases, in all cases but one they represented subclinical difficulties. No definite evidence was found to support the idea of restricting flying duties when INH is taken.

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STUDY 2

MENTAL STATUS EXAMINATION

PROCEDURE

Three mental status tests were performed--serial subtraction, oral recall and judgment. Although these and other similar tests are not standardized, they are part of a complete neurological examination.

Serial Subtraction - Subjects were instructed to begin at 100 and subtract by 7 serially and progress to zero. They were instructed to perform this mentally and give the examiner the answer for each subtraction. The responses were recorded along with the time required.

A score of one point was awarded for each correct answer given by the subject. Points were accumulated until an error was committed. For example, if a subject gave the following sequence: 93-86-79-72-53, his score would be four.

Oral Recall - Oral recall was tested by reading aloud to the subjects a paragraph containing 26 items of information. The paragraphs were similar in structure but varied in content at each test. The presentation was made in a standardized manner with no repetition of any part. At the 12 month-test a paragraph of 27 items was inadvertently used. Subjects were asked to recall everything they could. A score of one point was given for each fact recalled correctly and with the proper association, or for an acceptable synonymous fact, showing retention of the basic nature of the fact. No score was given for any other response.

Judgment - Judgment was tested by presenting the subjects with a situational problem. They were requested to relate the action they would take if placed in that situation. The response was evaluated in terms of the responses usually obtained, and a rating of normal, above normal or below normal was made.

RESULTS

Serial Subtraction - The means and standard deviations for the serial subtraction scores are presented in Table 7. The data for the 6- and 12-month subjects are presented separately.

TABLE 7

STATISTICAL ANALYSIS OF MENTAL STATUS TEST

	MEAN SCORES					STANDARD DEVIATIONS				
	6-Month Group		12-Month Group			6-Month Group		12-Month Group		
	Control	6 Mos.	Control	6 Mos.	12 Mos.	Control	6 Mos.	Control	6 Mos.	12 Mos.
Serial Subtraction - Score	5.9	7.6	7.1	9.8	9.1	5.8	3.4	5.8	5.1	5.5
Serial Subtraction - Time	54.9	49.3	49.7	48.3	53.8	22.5	19.1	19.7	18.4	37.7
Oral Recall - Score	8.4	10.7	8.6	11.5	9.0	3.0	3.1	2.5	3.4	3.5

**p<.01

The results indicate a slight improvement in serial subtraction scores from control to 6 months in both the 6- and 12-month subjects. This improvement is maintained at 12 months. None of these differences were found to be statistically significant in a one-way classification analysis of variance (ANOVA).

The serial subtraction time scores also showed improvement from control to 6 months in both subject groups. In the 12-month subjects the improvement was not maintained. These differences were again not statistically significant in an ANOVA. Summary tables for the ANOVA will be found in Appendices 2 and 3.

Oral Recall - Table 7 presents the means and standard deviations of the oral recall test for the 6- and 12-month subjects. The results indicate an improvement in oral recall from control to 6 months which was not maintained at 12 months. A one-way classification ANOVA showed a significant difference in recall scores over trials ($p<.01$). Individual tests of mean recall scores showed that the source of this difference was that the 6-month scores differed from the control and 12-month scores ($p<.01$) and that the control and 12-month scores did not differ from each other (See Appendix 5).

An accuracy score was also derived by subtracting the number of synonymous answers from the number of correct answers and dividing the difference by the total number recalled. The resulting score was expressed as a percentage.

The mean percent recalled scores for both the 6- and 12-month subjects was about 37%. Scores for both groups paralleled the results shown for the raw scores which showed an increase at 6 months. The mean accuracy scores ranged from 95 to 97%. There was no change from the control scores in either group.

Judgment - Only two subjects out of the entire group of 28 showed a slight decrease in judgment over the 12 months of therapy.

DISCUSSION

The oral recall test was designed to assess short term memory and serial recall. Although the paragraph stimuli were not part of a standardized test, an attempt was made to equate the number, type, and order of presentation of names, dates and places mentioned in the paragraph (See Appendix 6 for the paragraphs employed).

There is no readily apparent explanation for the significant increase

in the 6-month scores which were not maintained. One or both of the following factors may account for the difference.

First, the 6-month stimulus material may have been less difficult than the others.

Second, several subjects showed greater interest in this test than in other mental status tests. This could account for an increase at 6 months, but additional explanations would be required to explain the decrease at 12 months.

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STUDY 3

ELECTROENCEPHALOGRAPHIC EXAMINATION

METHOD

Apparatus and Procedure - Routine clinical EEG's were performed on a Grass Model 3, eight channel electroencephalograph. Grass cup electrodes were applied and secured to the head with bentonite paste according to the 10-20 International System of electrode placement. Seven montages including monopolar, bipolar, anterior to posterior, lateral, parasagittal and coronal runs covering all areas of the head were made. The monopolar reference electrodes were affixed to the ears. Three minutes of hyperventilation were recorded. The subjects were not sleep deprived and no attempt was made to obtain sleep tracings. Attempts were made in all cases to maintain filter settings of HLF 70, LLF 1.

Data Analysis - Two types of analyses were performed. First, a routine clinical analysis was done in which the tracings were read as normal, borderline or abnormal. Second, a subclinical analysis was done in which more detailed and quantified measures of the EEG were sought.

For the subclinical analysis, the following criteria were employed:

Delta Rhythm - 0-4 Hz

Theta Rhythm - 4-8 Hz

Well Developed Alpha - Rhythm in the 8-13 Hz range which is more or less sinusoidal, smooth in waveform and clearly discernible from the other rhythms present. (See Figure 1A.)

Other Alpha - Rhythm in the 8-13 Hz range of low amplitude, contaminated with other rhythms, irregular and not clearly seen. A clear distinction with well developed alpha was usually obvious. (See Figure 1B.)

Beta Rhythm - More than 13 Hz.

Organization - EEG data often contain several rhythms which mix or override each other, producing an irregular pattern

FIGURE 1A

WELL DEVELOPED ALPHA

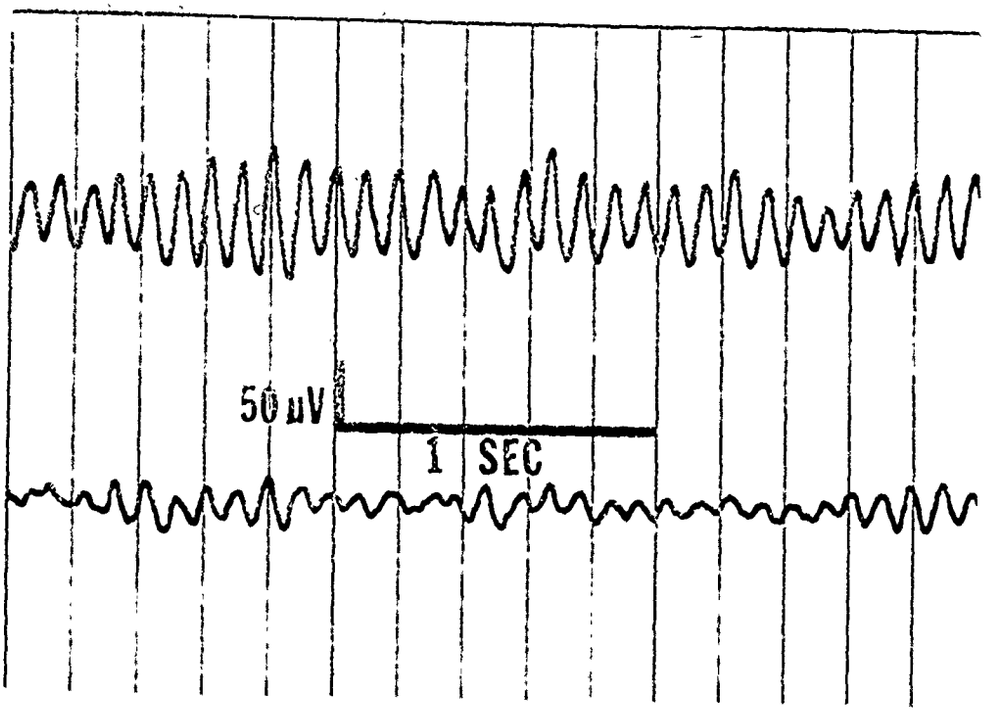
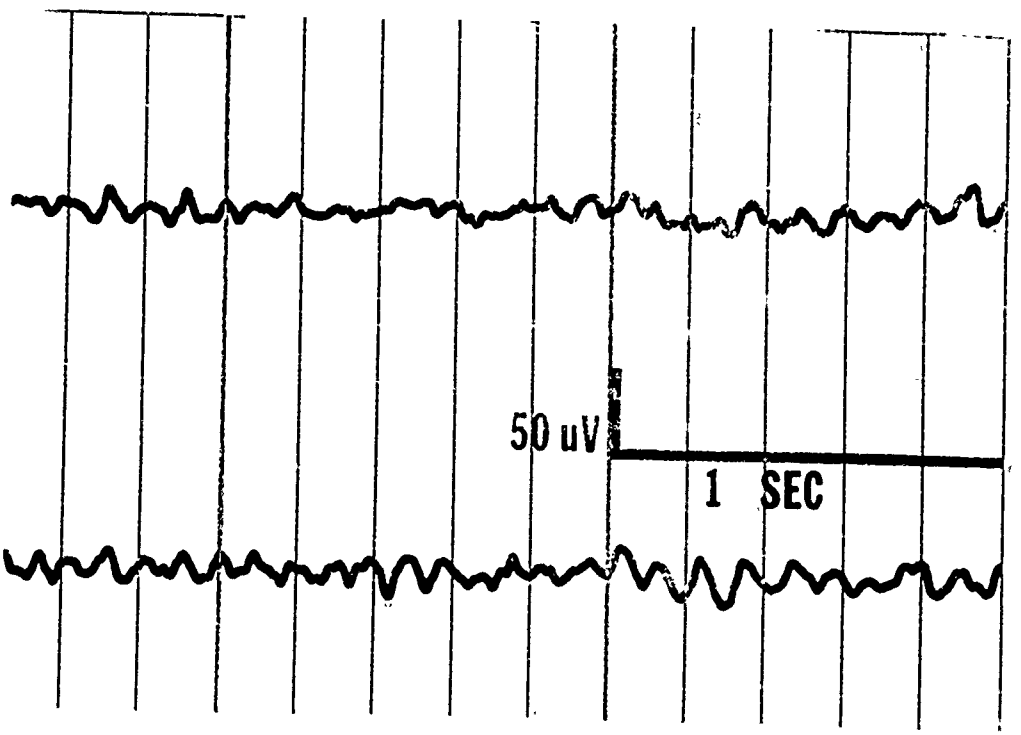


FIGURE 1B

OTHER ALPHA



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of frequency and amplitude. On the other hand, there is often a dominant frequency with little variation in amplitude which produces a smooth, regular appearance. The term "organization" is used to denote this difference. The first example would be classified as poorly organized; the second as well organized.

Focus - The area where a rhythm is most prominent and highest in amplitude.

Extent - The total area where a rhythm is seen.

Buildup - The EEG response to three minutes of hyperventilation which consists of slowing of frequency and increase in amplitude.

Asymmetry - A difference in EEG patterns over homologous brain areas. The side containing the greatest degree of the parameter is considered to be the side possessing the asymmetry.

Shift - A change in location from one area of a hemisphere to another of an EEG parameter. To be considered a shift, the size of the area had to remain the same.

• Phase 1 - Three types of observations were made on the data in Phase 1. The first of these involved recording the presence of various frequencies of asymmetries (right and left) in each channel. In the case of beta rhythm nearly all channels contained frequencies in this range. Therefore, only beta rhythm, which was higher than the background in amplitude and stood alone, was counted.

The second involved a forced choice ranking procedure which was applied to the data on buildup, organization, amplitude and the amount of each frequency. The forced choice ranking involved direct comparison of each montage of the control, 6-month and 12-month record for each subject.

The third involved ten measurements of alpha frequency in the first montage (lateral monopolar).

Sometimes artifact or sleep occurred throughout a channel. When this occurred the data were handled as if the activity in question were present, but no ranking was done for the montage in which it occurred.

• Phase 2 - In Phase 2 of the analysis the following concept of "change" was employed. Since the 6- and 12-month measures may be higher or lower than control and vary independently of each other, many combinations of conditions may result. Only three were considered in this study as a valid change over the course of therapy.

1. Progressive increase or decrease.

2. Control and 6-month measures were identical, but the 12-month measure was increased or decreased.

3. A change from control at six months with the change persisting at some degree at 12 months (a constant shift).

The data on presence of each frequency and on asymmetries (which were recorded for each channel) were then organized according to the location on the head. Using this organization the following parameters were derived: Shifts, determination of focus and extent of focus, determination of extent of the various frequencies. The areas of the head were defined by the position of the EEG electrodes.

For the data on the forced choice ranking (involving amplitude, organization and amount of each frequency), each montage of each EEG was classified as showing a "change" or "no change" according to the following scheme.

Since there were seven montages in each EEG, many combinations of scores for each parameter were possible. In order to determine whether an overall change in the parameter should be noted, all the possible combinations were listed in descending order from the situation where all seven montages showed the same change, and an overall change was obvious to the situation where all montages showed no change. The number of EEG's showing each combination was tabulated as well as the number of montages showing progressive changes in each combination.

In order to determine whether or not an overall change occurred, a cutoff point was sought. A cutoff was made at the point where 50% or more of the montages showed the change. Since there was no obvious gap there and since nearly half the number of observations lay below the line, it was decided to search for an additional discriminator. An obvious one was found and used.

According to this scheme, if a change was noted in more than 50% of the montages and two or more of the changes were progressive (12

mo > 6 mo > control), an overall change was recorded for the EEG. If not, no change was recorded.

Since the data on buildup involved only one measurement, these and the data of the third observation involving alpha frequency, were recorded as a change or no change, according to the definition outlined in the beginning of this section.

• Phase 3 - In Phase 2 the data were categorized according to whether a change occurred. In Phase 3 the nature of the change was examined (increase or decrease). These determinations were recorded in tabular form for each of the parameters.

The data which were organized according to location on the head were recorded as a change from one area to another, rather than an increase or decrease in one area.

Since the EEG electrodes defined a number of subdivisions of the head in the anterior to posterior direction and since medial or lateral shifts could occur in any or all subdivisions, several medial-lateral shifts could occur. Rather than attempting to derive an overall medial-lateral shift measure, a shift was recorded in each area where it occurred.

The nature of this data was such that no meaningful statistical analysis could be performed. Therefore, overall changes in the EEG were considered according to two criteria: (1) More than 50% of the subjects had to show a change and (2) Since changes in opposite and mutually exclusive directions occurred, twice as many subjects had to show a change in one direction as the number of subjects showing a change in the opposite direction. Both the above criteria had to be met for a change to be considered to have occurred in a given parameter. For example, if eight of 20 subjects showed no change in alpha frequency, seven showed an increase and five showed a decrease, no overall change in alpha frequency would be considered to have occurred. However, if five subjects out of 20 showed no change in alpha frequency, 11 showed an increase and four showed a decrease, an overall increase in alpha frequency would be recorded.

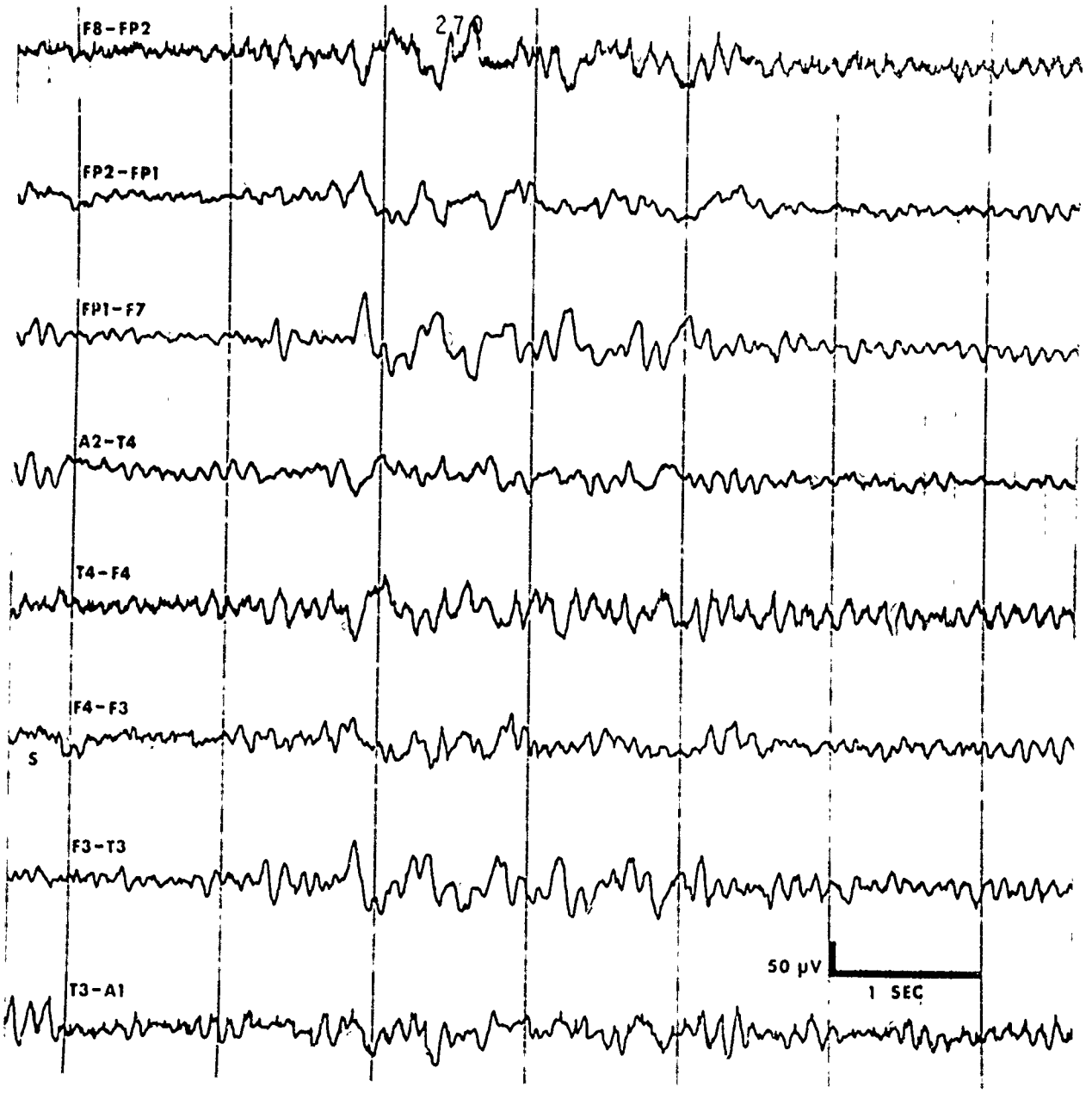
RESULTS

Clinical - Only one subject showed an EEG abnormality. Two others showed some abnormality at some time during the study.

The first subject had a normal control EEG. At six months a definite burst of slow activity was noted, which was labeled "paroxysmal." This is

FIGURE 2

PAROXYSMAL BURSTS OF SUBJECT



illustrated in Figure 2. Considerably more buildup was noted on hyperventilation at this time. This record was considered suspicious. At 12 months, two paroxysmal bursts of slowing were seen in the resting record and several more during hyperventilation. This record was considered as "borderline abnormal." Thus, one EEG abnormality was found, yielding an incidence of 3.6%.

The other subjects that showed some abnormality only showed it at one of the three testing periods. The nature of the abnormality in each case was slowing, at the control EEG in one case, and at the 6-month EEG in the other. All other EEG's on these subjects were normal.

Subclinical - The results of the subclinical analyses are presented in Tables 8 to 10. The derivation of this information and definitions of terms are given in the data analysis section.

In general, the following changes were noted:

Alpha - There was an increased extent of alpha focus, principally in the medial and parasagittal areas.

Beta - There was an increased amount seen with no change in extent. More asymmetry was noted. The asymmetry was widespread, seen in the frontopolar, frontal, posterior temporal and parietal areas. The medial, lateral and parasagittal areas all demonstrated the increase.

Theta - An increased amount was noted.

Buildup - Buildup was increased in the 6-month group only, although the change was noted in 86% of that group.

DISCUSSION

One subject had a clearly abnormal pattern of EEG's in the study. Two other subjects had what would be considered abnormal EEG's, but they were of a transient nature. It could be argued that these subjects should have been considered to have abnormal patterns. In the clinical domain transient abnormalities are reported.

However, it was elected not to consider this as an EEG change due to INH because the EEG is a variable measure within the same subject, and the transient changes may be reflecting just this. In the one subject manifesting a clear progression of change, the possibility of this being a normal variation was much smaller.

TABLE 8

CHANGES IN EEG PARAMETERS

Parameter	Group	% Subjects Showing:			Type Change Noted - %		
		Increase	Decrease	No Change	Progressive	6+12 Mos.	12 Mos. Only
ALPHA - Frequency	12 Mo.	20	20	60	13	38	50
	6 Mo.	0	29	71			
Extent	12 Mo.	60	10	30	45	5	50
	6 Mo.	29	57	14			
Extent of Focus	12 Mo.	60	5	35	8	0	92
	6 Mo.	29	14	57			
Amount	12 Mo.	35	40	25	--	--	--
	6 Mo.	29	57	14			
Overall Asymmetry	12 Mo.	35	30	35	38	8	54
	6 Mo.	29	57	14			
Right Sided	12 Mo.	0	5	95	0	0	100
	6 Mo.	14	14	71			
Left Sided	12 Mo.	20	5	75	0	0	100
	6 Mo.	14	14	71			
WELL DEVELOPED ALPHA - Extent	12 Mo.	70	10	20	19	13	69
	6 Mo.	29	57	14			
BETA - Extent	12 Mo.	35	20	45	0	0	100
	6 Mo.	43	0	57			

TABLE 8 (Continued)

CHANGES IN EEG PARAMETERS

Parameter	Group	% Subjects Showing:			Type Change Noted - %		
		Increase	Decrease	No Change	Progressive	6+12 Mos.	12 Mos. Only
Extent of Focus	12 Mo.	50	30	20	0	0	100
	6 Mo.	29	0	71			
Amount	12 Mo.	55	5	40	--	--	---
	6 Mo.	57	14	29			
Overall Asymmetry	12 Mo.	75	15	10	50	6	34
	6 Mo.	71	14	14			
Right Sided	12 Mo.	25	0	75	20	0	80
	6 Mo.	0	0	100			
Left Sided	12 Mo.	30	10	60	0	13	88
	6 Mo.	29	0	71			
THETA - Extent	12 Mo.	40	30	30	21	7	71
	6 Mo.	57	43	0			
Extent of Focus	12 Mo.	55	15	30	0	7	93
	6 Mo.	14	29	57			
Amount	12 Mo.	35	10	55	--	--	---
	6 Mo.	71	29	0			
Overall Asymmetry	12 Mo.	50	15	35	23	23	54
	6 Mo.	14	57	29			

TABLE 8 (Continued)

CHANGES IN EEG PARAMETERS

Parameter	Group	% Subjects Showing:			Type Change Noted - %		
		Increase	Decrease	No Change	Progressive	6+12 Mos.	12 Mos. Only
Right Sided	12 Mo.	0	10	90	0	0	100
	6 Mo.	0	14	86			
Left Sided	12 Mo.	15	0	86	0	0	100
	6 Mo.	29	14	57			
DELTA - Extent	12 Mo.	5	40	55	33	0	67
	6 Mo.	43	14	43			
Overall Asymmetry	12 Mo.	5	10	85	0	0	100
	6 Mo.	14	14	71			
Right Sided	12 Mo.	0	5	95	0	0	100
	6 Mo.	0	0	100			
Left Sided	12 Mo.	0	0	100	0	0	0
	6 Mo.	14	0	86			
AMPLITUDE -							
Amount	12 Mo.	0	30	70	--	--	---
	6 Mo.	43	57	0			
Overall Asymmetry	12 Mo.	20	25	55	11	22	67
	6 Mo.	29	57	14			

TABLE 8 (Continued)

CHANGES IN EEG PARAMETERS

Parameter	Group	% Subjects Showing:			Type Change Noted - %		
		Increase	Decrease	No Change	Progressive	6+12 Mos.	12 Mos. Only
Right Sided	12 Mo.	5	5	90	0	0	100
	6 Mo.	14	0	86			
Left Sided	12 Mo.	0	0	100	0	0	0
	6 Mo.	0	0	100			
BUILDUP	12 Mo.	25	25	50	50	0	50
	6 Mo.	86	14	0			
ORGANIZATION	12 Mo.	30	15	55	--	--	---
	6 Mo.	29	43	29			
ORGANIZATIONAL ASYMMETRY	12 Mo.	20	0	80	--	--	---
	6 Mo.	0	14	86			

TABLE 9

PARAMETER SHIFTS

Parameter	Group	PERCENT OF SUBJECTS SHOWING SHIFTS				
		Medial	Lateral	Anterior	Posterior	No Shifts
Alpha	12 Mo.	0	5	0	0	95
	6 Mo.	0	14	0	0	86
Alpha Focus	12 Mo.	5	5	15	0	75
	6 Mo.	14	0	0	0	86
Alpha Asymmetry	12 Mo.	5	5	15	10	65
	6 Mo.	14	14	14	0	57
Developed Alpha	12 Mo.	5	0	10	0	85
	6 Mo.	14	0	0	14	71
Developed Alpha Focus	12 Mo.	0	0	0	0	100
	6 Mo.	0	0	0	0	100
Beta	12 Mo.	10	5	0	5	80
	6 Mo.	0	14	0	14	71
Beta Focus	12 Mo.	0	5	5	5	85
	6 Mo.	0	14	0	14	71
Beta Asymmetry	12 Mo.	0	0	15	0	85
	6 Mo.	0	0	14	0	86
Theta	12 Mo.	5	5	5	5	80
	6 Mo.	0	14	0	14	71
Theta Focus	12 Mo.	25	5	20	20	30
	6 Mo.	14	14	14	14	43
Theta Asymmetry	12 Mo.	0	10	5	0	85
	6 Mo.	14	0	0	0	86

TABLE 10

CHANGES IN EEG PARAMETERS BY AREA

	Change	Group	% Changes Seen In:										
			Frontal Pole	Frontal	Posterior Frontal	Anterior Temporal	Mid-Temporal	Posterior Temporal	Parietal	Occipital	Medial	Parasagittal	Lateral
Alpha Extent	Increase	12 Mo	45	40	20	25	5	5	10	5	83	100	86
		6 Mo	14	14	14	14	0	0	0	0	25	100	20
	Decrease	12 Mo	10	5	0	0	5	0	0	5	17	0	14
		6 Mo	57	14	0	0	14	0	0	14	75	0	80
Extent of Focus	Increase	12 Mo	0	20	40	5	5	15	30	30	71	59	41
		6 Mo	0	0	29	0	43	29	14	0	100	67	63
	Decrease	12 Mo	0	5	0	0	15	20	25	35	29	41	59
		6 Mo	0	14	0	0	14	29	0	0	0	33	38
Asymmetry	Increase	12 Mo	20	15	40	40	45	30	50	20	48	51	53
		6 Mo	29	29	43	0	43	0	57	14	25	63	47
	Decrease	12 Mo	30	30	25	30	25	50	35	20	52	49	47
		6 Mo	14	2[illegible]	29	43	14	43	43	29	75	38	53
Developed Alpha Extent	Increase	12 Mo	30	40	60	30	30	20	30	35	68	93	72
		6 Mo	14	29	43	14	29	29	14	0	30	70	56
	Decrease	12 Mo	5	15	15	0	15	15	15	20	32	7	28
		6 Mo	14	29	29	29	29	0	29	14	70	30	44
Beta - Extent	Increase	12 Mo	30	10	35	20	30	20	25	20	71	59	72
		6 Mo	29	14	29	14	29	0	57	14	60	100	71
	Decrease	12 Mo	5	10	10	10	20	15	15	25	29	41	28
		6 Mo	0	0	29	0	0	14	0	14	40	0	29

TABLE 10 (Continued)

CHANGES IN EEG PARAMETERS BY AREA

	Change	Group	% Changes Seen In:										
			Frontal Pole	Frontal	Posterior Frontal	Anterior Temporal	Mid-Temporal	Posterior Temporal	Parietal	Occipital	Medial	Parasagittal	Laturai
Extent of Focus	Increase	12 Mo	35	40	35	25	15	5	15	15	52	66	45
		6 Mo	14	0	14	0	14	0	0	0	100	100	33
	Decrease	12 Mo	20	45	20	25	15	0	5	0	48	34	55
		6 Mo	14	14	0	0	0	0	0	0	0	0	66
Asymmetry	Increase	12 Mo	65	85	70	25	40	45	55	20	82	83	85
		6 Mo	29	43	43	14	29	14	29	[illegible]	100	70	67
	Decrease	12 Mo	15	0	20	15	10	15	20	15	18	17	15
		6 Mo	0	14	14	0	0	14	0	[illegible]	0	30	33
Theta - Extent	Increase	12 Mo	55	35	45	20	35	45	40	35	64	48	59
		6 Mo	0	14	29	29	57	29	57	14	23	62	63
	Decrease	12 Mo	25	25	40	35	30	25	30	45	35	52	41
		6 Mo	57	14	29	29	29	14	43	[illegible]	77	38	37
[illegible] of Focus	Increase	12 Mo	30	35	30	35	10	20	10	[illegible]	78	54	59
		6 Mo	14	29	14	0	29	0	14	[illegible]	29	50	33
	Decrease	12 Mo	15	25	20	20	10	[illegible]	20	[illegible]	22	46	41
		6 Mo	0	29	14	29	29	[illegible]	14	[illegible]	71	50	67
Asymmetry	Increase	12 Mo	20	30	25	30	25	40	25	[illegible]	87	67	61
		6 Mo	0	29	57	0	29	0	43	[illegible]	80	33	50
	Decrease	12 Mo	15	10	15	5	25	[illegible]	[illegible]	[illegible]	13	33	39
		6 Mo	14	43	29	[illegible]	29	29	29	[illegible]	20	67	50

TABLE 10 (Continued)

CHANGES IN EEG PARAMETERS BY AREA

	Change	Group	% Changes Seen In:										
			Frontal Pole	Frontal	Posterior Frontal	Anterior Temporal	Mid-Temporal	Posterior Temporal	Parietal	Occipital	Medial	Parasagittal	Lateral
Delta - Extent	[illegible]ease	12 Mo	5	20	15	0	0	0	0	5	45	13	20
		6 Mo	14	29	29	0	14	0	14	14	44	50	25
	Decrea[illegible]	12 Mo	20	30	35	25	20	30	25	20	55	87	80
		6 Mo	14	29	29	0	0	14	14	0	56	50	75
Asymmetry	Increase	12 Mo	0	0	15	0	0	5	5	0	20	7	11
		Mo	14	14	14	0	0	0	0	0	0	60	0
	Decrease	Mo	10	25	25	10	10	25	35	10	80	93	89
		Mo	0	0	14	14	0	0	14	0	0	40	100
Amplitude Asymmetry	Increase	12 Mo	5	10	25	5	15	30	25	20	29	58	34
		6 Mo	0	0	29	0	0	14	29	0	50	42	36
	Decrease	12 Mo	10	25	25	10	10	25	35	10	71	42	66
		6 Mo	14	14	29	29	0	29	15	5	50	58	64
Organization Asymmetry	Increase	12 Mo	0	0	0	0	0	0	15	5	100	100	50
		6 Mo	0	0	0	0	0	0	0	0	0	0	0
	Decrease	12 Mo	0	0	0	0	0	0	5	0	0	0	50
		6 Mo	0	0	0	0	0	14	0	0	0	100	100

In this one subject with progressive abnormalities, the change consisted of the appearance of paroxysmal bursts at the 6 and 12 month exams. Paroxysmal bursts are non-specific phenomenon defined as sudden short appearances of activity, obviously different than the other activity on the page and usually present in all leads. In most cases the paroxysmal activity consists of slower frequency waves and/or spikes. It is most compatible with seizure disorder [illegible] and during hyperventilation in the normal individual. As in all EEG phenomena this change may be seen in an individual who is perfectly normal clinically and does not imply that the subject has seizures.

Paroxysmal slowing as well as other EEG correlates of seizures are reported to occur with INH administration. In the present study only one case of progressive paroxysmal slowing was found. It is not known whether or not this change might not have occurred normally, or whether it was due to some other cause. This subject also was classified as "possible" neuropathy, and this clinical evidence, together with the fact that the EEG change was progressive, indicates that he was indeed experiencing neurological side effects of INH.

The remaining EEG analysis which has been called subclinical analysis was done in an effort to extract the maximum amount of information from the data on hand. Short of spectral analysis or some other computerized techniques, the authors are unaware of another study utilizing this approach. While the results of the present study may not have any particular clinical significance, it is hoped that as our knowledge of EEG expands we may one day understand the meaning of changes such as we describe here. With this hope of contribution to our knowledge in the future and for the interest it may have for the present reader, the analysis was undertaken. We emphasize again that the significance of this analysis is unknown and no valid EEG change is being suggested.

In addition to the above, another factor of importance should be noted. Throughout the analysis, subjectivity is dominant. The definitions of change and significance as detailed in the report were purely arbitrary. A knowledge of variation of normal EEG patterns over time does not exist at this level and a control group was not included for comparison. Judgments about the EEG's were totally subjective. The designations of well-developed alpha and [illegible] activity were generated by the authors for purposes of discussion and should be taken in that light only.

For all these reasons no statistical analysis was done on the final data, since more significance would have been implied than was warranted. The final results were merely presented with an attempt at interpretation.

STUDY 4

VISUAL EVOKED POTENTIAL

METHOD

Apparatus and Procedure - Visual evoked potentials were recorded on each subject. The stimulus consisted of 100 flashes of light from a Grass PST 2100 bulb at the rate of one flash per second. The flashes were controlled by a Grass PS3 photo stimulator unit. The intensity was set at 16, which corresponds to a maximum flash intensity of 1,500,000 candella. The lamp was placed directly in front of the subject's face, 15 cm from the nose. No shielding of the face of the lamp nor interval filtering of the flash was done. The subject was requested to keep his eyes closed and to look through his eyelids in the direction of the flash. An attempt was mde to maintain alertness by the use of high ambient noise levels and verbal stimulation.

Only 100 light stimuli were given, and the VEP's were recorded from four different areas simultaneously. Recordings were made in the bipolar mode from four electrodes placed as follows: O_z - over the inion; P_z - in the midline parietal area corresponding exactly to the placement of the 10-20 International System; O_1 and O_2 - 3 cm lateral and 3 cm superior to O_z. VEP's were recorded between O_1 and O_2, O_2 and O_z, O_1 and O_2 and O_z and P_z (Channels 1, 2, 3 and 4 respectively).

A pulse artifact corresponding to each flash from the PS3 stimulator and the subject's EEG response were recorded on paper and magnetic tape.

An Ampex SP300 recorder was employed with recordings made in the FM mode. The output from the Grass EEG machine was fed through a voltage divider system to the input of the recorder. The input sensitivity of the recorder was adjusted so that a 100 microvolt calibration signal from the EEG machine produced a peak to peak voltage deflection of 1.5 v as measured on a CRO monitor at the output of the recorder. The stimulus artifact was recorded on a separate data channel, with the input sensitivity level adjusted in the same manner.

The raw data were processed off-line. The output of the Ampex recorder was fed into a Nuclear Data Inc. Model ND-800 Enhancetron 1024 for averaging. The output of the averager was viewed on a Tektronix Type 503 oscilloscope. The potential was written out on a Hewlett-Packard Model 7000 AM XY recorder.

Data Analysis - The potentials were inspected visually to detect any obvious changes. None were detected. Consequently, a more critical analysis was undertaken.

First, a baseline was drawn for each VEP. Since there was apparent drift in some cases, the best-fitting baseline was selected. In most cases it was an obvious one. A straight horizontal or nearly horizontal line was the best fit in most cases. Most potentials contained sinusoidal deflections. The points that bisected these deflections, along with the initial starting point of the deflection, were used to determine the baseline.

Second, the potentials were divided into three parts corresponding to the: (1) Specific, early or primary complex; (2) non-specific, secondary complex or "main" discharge; (3) the after discharge. In many cases the points of division were obvious, based on a change in character of the complexes, amplitude of the waves, baseline width of the waves, etc. When the division was not obvious the points were located by identifying the wave which corresponded to wave five (according to Gestaut) and, with this, locating waves three and six. Wave five was identified as the one with the largest amplitude, the most complexity or the latency of approximately 130-200 mSec.

Vertical lines were drawn bisecting waves three and six, and these lines were used as division points. Both systems resulted in approximately the same division points.

When the VEP was thus divided, the amplitude, complexity and width of each section were determined. The amplitude measurements were in arbitrary units and represented the peak to peak amplitude of the largest wave within the complex. "Complexity" was defined as the number of changes in polarity in the deflection occurring within the division. In determining whether a change in polarity of deflection represented a wave, it was required that it either crossed the baseline or was the point of an obvious change in overall trend. Plateaus formed without reversal of polarity were not counted, nor were simple notches on a large wave. Latencies to the peak deflection of the VEP were also determined.

In the measurement of peak deflection latency, it was found that, in general, one wave was largest in amplitude. Rarely, two deflections of equal amplitude were found. In these cases the wave corresponding most closely to the established pattern for that channel was selected for measurement. The peak deflection was normally, but not always, wave five as defined by previous criteria.

The data from each channel were analyzed separately. A mean and

standard deviation were computed for each measurement. A separate one-way classification ANOVA was performed on the data from the 12-month subjects. Where two or more measures were derived, they were analyzed separately by trials (0, 6, 12 months).

In one VEP reliable measurement of the latency to peak deflection could not be made. A value was estimated for the analysis according to the method outlined in Winer.[104]

Twenty-four VEP's were suitable for analysis. Eighteen in the 12-month group and six in the 6-month group.

RESULTS

The means and standard deviations of the nine (9) measurements are presented in Table 11. Significant differences between means are indicated. The analysis of variance and post hoc tests on which these differences are based are presented in Appendices 2 to 49.

No grossly visible differences were noted in any of the VEP's.

Primary complex amplitude - There was an increase in primary complex amplitude in channels two and threeat six and 12 months. The difference in channel three was significant ($p<.05$). Post hoc tests demonstrated that the source of the difference was that both the 6 and 12 month scores differed significantly from control ($p<.05$), but not from each other. In channel two, the control amplitude was higher than either 6 or 12 months.

Primary complex complexity - There was a significant increase at 6 and 12 months in channel one ($p<.05$). All other channels showed an increase at 6 and 12 months, but none of these differences were significant.

Secondary complex latency - No significant changes nor trends were seen.

Secondary complex width - A significant decrease ($p<.05$) at decrease was found in channel one compared to the 12 month and control values. Channels three and four of the 12-month group and all channels of the 6-month group show the same decrease at 6 months.

Secondary complex latency to peak deflection - No significant changes nor trends were seen.

Secondary complexity amplitude - A significant increase at 12 months

TABLE 11

VISUAL EVOKED POTENTIALS

Parameter	12 Month Group n = 18 Mean	SD	6 Month Group n = 6 Mean	SD
Primary Complex				
Amplitude[1]				
Channel 1				
Control	12.33	8.68	11.17	7.17
6 Months	11.00	7.03	27.00	15.01
12 Months	15.78	14.01		
Channel 2				
Control	12.39	9.08	17.33	14.05
6 Months	20.94	14.24	18.00	9.10
12 Months	21.50	16.92		
Channel 3				
Control	14.89	8.11	16.33	14.64
6 Months	22.44*	11.13	16.17	9.33
12 Months	23.78*	11.64		
Channel 4				
Control	33.44	28.94	23.00	16.59
6 Months	27.61	22.97	44.17	14.73
12 Months	28.11	36.08		
Complexity				
Channel 1				
Control	2.44*	1.04	2.33	1.37
6 Months	3.67	1.85	3.67	1.03
12 Months	3.78	1.96		
Channel 2				
Control	3.17	1.25	2.00	.63
6 Months	3.67	1.85	3.83	.75
12 Months	3.50	1.69		
Channel 3				
Control	3.06	.87	3.67	.82
6 Months	3.83	1.42	4.00	.89
12 Months	3.28	1.74		

TABLE 11 (Continued)

VISUAL EVOKED POTENTIALS

Parameter	12 Month Group n = 18 Mean	SD	6 Month Group n = 6 Mean	SD
Channel 4				
Control	2.83	1.10	2.33	1.03
6 Months	3.28	1.07	2.67	1.21
12 Months	3.00	1.14		
Secondary Complex				
Latency to Beginning[3]				
Channel 1				
Control	74.72	19.96	65.83	11.58
6 Months	76.67	21.07	85.00	18.17
12 Months	70.00	29.46		
Channel 2				
Control	77.50	16.56	74.17	8.01
6 Months	72.22	19.50	87.50	12.14
12 Months	67.22	21.50		
Channel 3				
Control	71.39	16.96	70.00	8.94
6 Months	71.11	15.20	82.50	18.64
12 Months	68.61	19.99		
Channel 4				
Control	63.33	16.09	62.50	15.73
6 Months	70.56	23.45	77.50	31.10
12 Months	59.17	16.29		
Width[3]				
Channel 1				
Control	162.50	33.00	179.17	38.52
6 Months	146.94[4]*	36.83	143.33	26.96
12 Months	163.33	38.39		
Channel 2				
Control	150.00	34.39	150.00	33.91
6 Months	152.22	37.78	144.17	37.07
12 Months	154.44	43.99		

TABLE 11 (Continued)

VISUAL EVOKED POTENTIALS

Parameter	12 Month Group n = 18 Mean	SD	6 Month Group n = 6 Mean	SD
Channel 3				
Control	147.22	40.04	161.67	28.75
6 Months	134.72	34.28	140.83	34.27
12 Months	142.22	40.81		
Channel 4				
Control	161.39	35.31	156.67	9.83
6 Months	160.28	36.60	136.67	16.93
12 Months	162.50	41.56		
Latency to Peak Deflection[3]				
Channel 1				
Control	152.78	27.07	157.50	33.58
6 Months	150.00	35.31	175.83	37.61
12 Months	158.61	57.77		
Channel 2				
Control	147.17	42.35	148.33	29.44
6 Months	144.17	41.03	170.83	20.35
12 Months	148.61	54.58		
Channel 3				
Control	135.83	27.08	126.67	23.59
6 Months	152.78	38.81	150.83	28.88
12 Months	130.56	51.27		
Channel 4				
Control	143.06	32.50	150.00	18.17
6 Months	152.78	59.88	141.67	42.03
12 Months	141.39	40.83		
Amplitude				
Channel 1				
Control	40.94	31.20	56.67	33.01
6 Months	32.17	19.93	42.00	21.88
12 Months	82.28[4]*	74.27		

TABLE 11 (Continued)

VISUAL EVOKED POTENTIALS

Parameter	12 Month Group n = 18 Mean	SD	6 Month Group n = 6 Mean	SD
Channel 2				
Control	30.22	19.52	44.17	25.95
6 Months	34.11	17.91	41.33	21.20
12 Months	60.89*	47.56		
Channel 3				
Control	42.39	26.67	57.33	33.39
6 Months	38.28	23.27	41.83	33.87
12 Months	63.33*	34.25		
Channel 4				
Control	119.78	50.61	81.17	27.24
6 Months	79.78	41.11	93.33	54.37
12 Months	93.39	79.27		
Complexity				
Channel 1				
Control	4.56	1.76	4.00	1.10
6 Months	4.50	2.01	3.83	.98
12 Months	5.28	1.53		
Channel 2				
Control	4.39	1.94	3.33	.52
6 Months	4.56	1.85	4.83	1.72
12 Months	5.44	2.12		
Channel 3				
Control	5.50	1.72	4.83	1.60
6 Months	5.06	1.89	4.33	1.51
12 Months	4.72	1.45		
Channel 4				
Control	5.17	1.69	4.67	1.51
6 Months	5.44	1.46	4.33	1.21
12 Months	5.28	1.99		

TABLE 11 (Continued)

VISUAL EVOKED POTENTIALS

Parameter	12 Month Group n = 18 Mean	SD	6 Month Group n = 6 Mean	SD
After Discharge				
Amplitude				
Channel 1				
Control	17.00	11.92	24.33	12.40
6 Months	21.28	12.02	25.83	11.25
12 Months	33.82*	24.92		
Channel 2				
Control	19.33	12.15	25.67	17.49
6 Months	21.56	13.61	26.00	17.26
12 Months	26.67	21.00		
Channel 3				
Control	23.94	13.93	37.00	34.62
6 Months	26.78	13.55	29.00	19.91
12 Months	34.50	18.87		
Channel 4				
Control	64.17	32.32	46.67	24.55
6 Months	46.06	26.78	63.67	41.02
12 Months	51.67	50.04		
Complexity				
Channel 1				
Control	6.50	2.68	6.00	1.90
6 Months	8.33	2.45	6.83	.41
12 Months	7.83	2.62		
Channel 2				
Control	6.89	2.49	5.67	1.03
6 Months	8.17	3.31	6.50	2.07
12 Months	8.56	4.26		
Channel 3				
Control	8.00	2.59	6.67	2.58
6 Months	8.06	2.04	8.50	1.22
12 Months	9.44	3.90		

TABLE 11 (Continued)

VISUAL EVOKED POTENTIALS

Parameter	12 Month Group n = 18 Mean	SD	6 Month Group n = 6 Mean	SD
Channel 4				
Control	7.39	2.12	7.50	2.59
6 Months	7.61	2.43	7.17	1.47
12 Months	9.00	3.53		

[1]Amplitude is in relative units.

[2]Complexity refers to the number of changes in polarity within the complex.

[3]In milliseconds.

[4]The analysis of variance revealed a significant difference at the .01 level of confidence, but the source of the difference was identified only at the .05 level.

*p<.05

compared to control on 6 months was seen in three channels: Channel 2 ($p<.01$), channel 3 ($p<.05$), channel 4 ($p<.05$).

Secondary complex complexity - No significant differences nor trends were seen.

After discharge amplitude - A significant increase ($p<.05$) at 12 months compared to control and 6 months was found in channel one. Channels two and three also showed an increase in after discharge amplitude, but the increase was not statistically significant.

After discharge complexity - The 6 and 12 month values were higher than the control values in all channels of both groups. These differences were not found to be statistically significant, however.

DISCUSSION

The scattered significant differences that were found in the visual evoked potential data are difficult to interpret. It seems reasonable to expect that any real change occurring would be found in all channels. This was found to be the case regarding the complexity of the primary complex and the after discharge, but only in the primary complex were any of the differences significant. The more traditional measures of latency and amplitude did not show any change seen consistently in all channels.

One other finding is worthy of note. This is the three channels showing an increase in the amplitude of the secondary complex at twelve months. Although the fourth channel showed an opposite change, the overall trend might be considered as a [illegible] of LSD on the evoked potential.

The remaining changes are [illegible] any of support in other channels that no real change was demonstrated. Only the changes in complexity appear to be valid.

Certain changes in the method of recording evoked potentials could have been desirable. For example, the evoked potential would have been entirely destroyed [illegible] in the end. Consequently, the quality of [illegible]. Experience now favors the monopolar mode which would have been preferable and delineated changes more accurately. Although attempts were made to control [illegible] parameters, certain factors such as the level of [illegible] distractions, etc.,

could not be controlled and may have influenced the final potential. Variation of the psychological state of the subject is known to have considerable influence on the evoked potential. This variable was unknown in our subjects. Employment of several different levels of stimulus parameters such as flash intensity or frequency might have yielded more useful data. Finally, a calibration signal should have been employed. The relative amplitude measures of this study cannot be directly compared with other studies because absolute amplitude measures were not available.

The changes in complexity are difficult to interpret. The measuring technique employing artificial boundaries may have created a difference where none existed. It may be that deflections were counted as changes in polarity that were actually noise or some other physiologic event. However, it would then be expected that the secondary complex would contain as much as other sections and have been scored in the same way. On the other hand, the large amplitude of the secondary complex may be more effective in obscuring such noise or make it relatively less apparent. Assuming that the change is real, its meaning is obscure since our knowledge of the underlying physiology of the evoked potential is incomplete.

The reasons for the other significant changes are unclear. It is possible that they are indicative of trends which would have been found, had different methods been employed in the present study. Changes in the dose of INH given or in the methodology as detailed above would be indicated. Since reliability was not established, it is likely that these changes are spurious values which represent normal variations.

Certainly, the techniques of analysis of the potentials employed in this study were different than those described in the literature. Because of methodological considerations and the fact that no grossly visible differences were seen, the usual methods of data analysis were not feasible. While no precedent could be found for the present method of data analysis, it was felt that some worthwhile ways of looking at VEP's, such as complexity, were contemplated.

Because of the large number of analyses which were performed, it is possible that some, but certainly not all, of the significant differences were "chance" significant differences.

SUMMARY AND CONCLUSIONS

Careful study of the results has disclosed several changes based on inspection of the data and on statistical analysis. Although it is impossible, for reasons detailed in this series of studies, to establish with certainty that INH was responsible for changes found, it is not possible to exclude INH as a cause either. The changes which were found were minimal and scattered and may have little or no significance. The clinical data probably raise the greatest question. Although the clinical findings were minimal in most cases, the significance is apparent, especially for aviators. The incidence of neuropathy is especially disturbing. Most flight surgeons would not want to allow aviators to fly with the probability of side effects which were found. Therefore, further studies are needed in order to establish whether the present data are spurious or would hold up for larger populations.

Meanwhile, although the results of the present study do not indicate that INH is innocuous and causes only nonsignificant effects, they also offer no conclusive evidence that should cause aviators to be grounded simply because INH is being administered.

In the final analysis it would seem wise to make judgment on an individual basis. The data strongly suggest that careful study of treated aviators is indicated. Policy statements on INH should await further studies.

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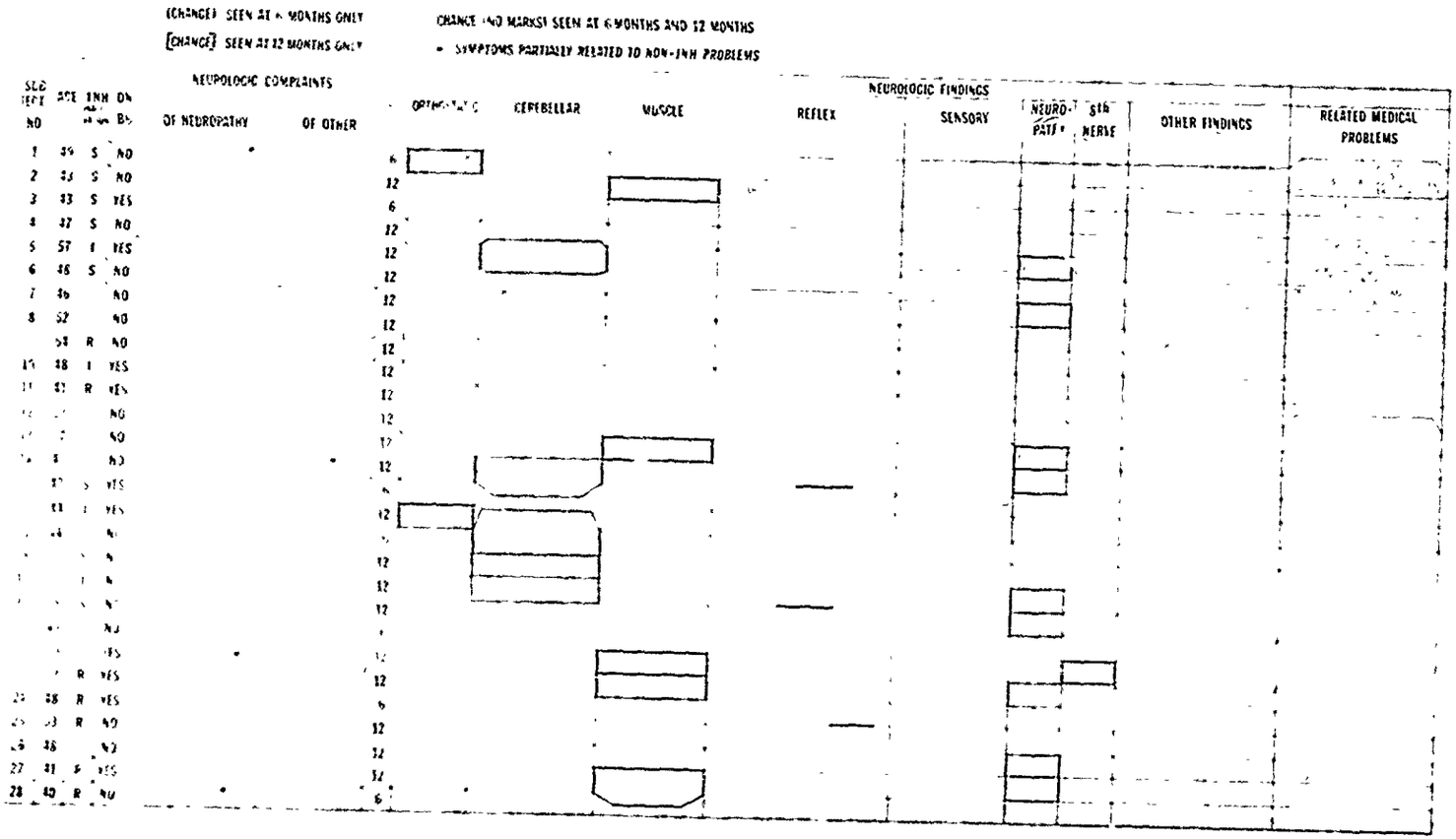
APPENDIX 1

SUMMARY OF CLINICAL SIGNS AND SYMPTOMS



APPENDIX 2

SUMMARY OF ANALYSIS OF VARIANCE
SERIAL SUBTRACTION - SCORE

Source	SS	df	MS	f
Between Subjects	773.94	20		
Within Subjects	1108.67	42		
Trials	80.03	2	40.02	1.56
Residual	1028.63	40	25.72	
TOTAL	1882.62	62		

APPENDIX 3

SUMMARY OF ANALYSIS OF VARIANCE
SERIAL SUBTRACTION - TOTAL TIME

Source	SS	df	MS	f
Between Subjects	27916.41	20		
Within Subjects	15412.67	42		
Trials	345.27	2	172.64	0.46
Residual	15067.40	40	376.69	
TOTAL	43329.08	62		

APPENDIX 4

SUMMARY OF ANALYSIS OF VARIANCE
ORAL RECALL - SCORE

Source	SS	df	MS	f
Between Subjects	435.27	20		
Within Subjects	264.00	42		
Trials	106.13	2	53.07	13.45**
Residual	157.87	40	3.95	
TOTAL	699.27	62		

**p<.01

APPENDIX 5

TESTS ON DIFFERENCES BETWEEN TOTALS
ORAL RECALL - SCORE

Ordered Tests	Control	12 Mo.	6 Mo.
TOTALS	181	188	242
Control 181	---	7	61**
12 Mo. 188		---	54**
6 Mo. 242			---

Truncated Range r	2	3
q.99 (r, 40)	3.82	4.37
$\sqrt{nMSres}$ q.99 (r, 40)	34.791	39.8002

**p<.01

APPENDIX 6

PARAGRAPH STIMULI FOR THE ORAL RECALL TEST

CONTROL - Mary Jones, age 23, of 157 North Walnut Street, Philadelphia, Pennsylvania, was seen wandering on the 3500 block of South Main Street, at 3:00 a.m. yesterday, the 13th of August 1959, having wrecked her 1957 Buick on the Johnson Bridge.

6 MONTHS - John Smith, age 46, of 235 South Cherry Street, Chicago, Illinois, was apprehended at the 1600 block of North Devon Street, at 1:00 a.m. yesterday, the 23rd of July 1969, after stealing a 1968 Cadillac from Nicholas Motor Company.

12 MONTHS - Bill Morris, age 29, of 758 West Holly Lane, Baltimore, Maryland, was observed at 2900 East Lombard Street at 5:00 p.m. yesterday, the 16th of October 1970. He had just left the 301 Club located next to the First National Bank Building.

APPENDIX 7

SUMMARY OF ANALYSIS OF VARIANCE
AMPLITUDE OF AFTER DISCHARGE - CHANNEL 1

Source	SS	df	MS	f
Between Subjects	5796	17		
Within Subjects	12388	36		
Trials	2756	2	1378	4.85*
Residual	9652	34	284	
TOTAL		53		

*p<.05

APPENDIX 8

SUMMARY OF ANALYSIS OF VARIANCE
AMPLITUDE OF AFTER DISCHARGE - CHANNEL 2

Source	SS	df	MS	f
Between Subjects	4154.81	17		
Within Subjects	9018.67	36		
Trials	509.04	2	254.52	1.02
Residual	8509.63	34	250.28	
TOTAL	13665.48	53		

APPENDIX 9

SUMMARY OF ANALYSIS OF VARIANCE
AMPLITUDE OF AFTER DISCHARGE - CHANNEL 3

Source	SS	df	MS	f
Between Subjects	6580.37	17		
Within Subjects	6972.66	36		
Trials	1074.48	2	537.24	3.10
Residual	5898.19	34	[illegible].48	
TOTAL	13553.64	53		

APPENDIX 10

SUMMARY OF ANALYSIS OF VARIANCE
AMPLITUDE OF AFTER DISCHARGE - CHANNEL 4

Source	SS	df	MS	f
Between Subjects	44165.26	17		
Within Subjects	31438.67	36		
Trials	3094.49	2	1547.25	1.86
Residual	28344.18	34	833.65	
TOTAL	157248.07	53		

APPENDIX 11

SUMMARY OF ANALYSIS OF VARIANCE
AMPLITUDE OF SECONDARY COMPLEX - CHANNEL 1

Source	SS	df	MS	f
Between Subjects	40230.09	17		
Within Subjects	102630.67	36		
Trials	25779.70	2	12889.85	5.70**
Residual	76850.97	34	2260.32	
TOTAL	142850.76	53		

**p<.01

APPENDIX 12

SUMMARY OF ANALYSIS OF VARIANCE
AMPLITUDE OF SECONDARY COMPLEX - CHANNEL 2

Source	SS	df	MS	f
Between Subjects	10571.70	17		
Within Subjects	49846.67	36		
Trials	10571.70	2	5285.85	4.51*
Residual	39810.97	34	1170.91	
TOTAL	60418.37	53		

*p<.05

APPENDIX 13

SUMMARY OF ANALYSIS OF VARIANCE
AMPLITUDE OF SECONDARY COMPLEX - CHANNEL 3

Source	SS	df	MS	f
Between Subjects	12780	17		
Within Subjects	34960	36		
Trials	6500.11	2	3250.06	3.88*
Residual	28459.89	34	837.06	
TOTAL	76199.89	53		

*p<.05

APPENDIX 14

SUMMARY OF ANALYSIS OF VARIANCE
AMPLITUDE OF SECONDARY COMPLEX - CHANNEL 4

Source	SS	df	MS	f
Between Subjects	65884.31	17		
Within Subjects	12810	36		
Trials	14889.81	2	7444.91	2.24
Residual	113218.19	34	3329.95	
TOTAL	193992.31	53		

APPENDIX 15

SUMMARY OF ANALYSIS OF VARIANCE
WIDTH OF SECONDARY COMPLEX - CHANNEL 1

Source	SS	df	MS	f
Between Subjects	56616.66	17		
Within Subjects	19366.67	36		
Trials	9363.88	2	4681.94	15.94**
Residual	10002.79	34	294.20	
TOTAL	75983.33	53		

**p<.01

APPENDIX 16

SUMMARY OF ANALYSIS OF VARIANCE
WIDTH OF SECONDARY COMPLEX - CHANNEL 2

Source	SS	df	MS	f
Between Subjects	54750.00	17		
Within Subjects	24683.33	36		
Trials	2177.77	2	1088.89	1.65
Residual	22505.56	34	661.93	
TOTAL	79433.33	53		

APPENDIX 17

SUMMARY OF ANALYSIS OF VARIANCE
WIDTH OF SECONDARY COMPLEX - CHANNEL 3

Source	SS	df	MS	f
Between Subjects	45870.83	17		
Within Subjects	31100.00	36		
Trials	1425.00	2	712.50	.82
Residual	29675.00	34	872.79	
TOTAL	76970.83	53		

APPENDIX 18

SUMMARY OF ANALYSIS OF VARIANCE
WIDTH OF SECONDARY COMPLEX - CHANNEL 4

Source	SS	df	MS	f
Between Subjects	56987.50	17		
Within Subjects	16383.33	36		
Trials	44.44	2	22.22	
Residual	16338.89	34	430.56	.05
TOTAL	73370.83	53		

90

APPENDIX 19

SUMMARY OF ANALYSIS OF VARIANCE
COMPLEXITY OF PRIMARY COMPLEX - CHANNEL 1

Source	SS	df	MS	f
Between Subjects	43.3	17		
Within Subjects	90	36		
Trials	17.3	2	8.65	4.05*
Residual	72.7	34	2.14	
TOTAL	133.3	53		

*p<.05

APPENDIX 20

SUMMARY OF ANALYSIS OF VARIANCE
COMPLEXITY OF PRIMARY COMPLEX - CHANNEL 2

Source	SS	df	MS	f
Between Subjects	69.33	17		
Within Subjects	66	36		
Trials	2.33	2	1.17	.62
Residual	63.67	34	1.87	
TOTAL	135.33	53		

APPENDIX 21

SUMMARY OF ANALYSIS OF VARIANCE
COMPLEXITY OF PRIMARY COMPLEX - CHANNEL 3

Source	SS	df	MS	f
Between Subjects	62.83	17		
Within Subjects	42	36		
Trials	5.77	2	2.89	2.70
Residual	36.23	34	1.07	
TOTAL	104.83	53		

APPENDIX 22

SUMMARY OF ANALYSIS OF VARIANCE
COMPLEXITY OF PRIMARY COMPLEX - CHANNEL 4

Source	SS	df	MS	f
Between Subjects	17.26	17		
Within Subjects	46.67	36		
Trials	1.82	2	.91	.69
Residual	44.85	34	1.32	
TOTAL	63.95	53		

APPENDIX 23

SUMMARY OF ANALYSIS OF VARIANCE
COMPLEXITY OF SECONDARY COMPLEX - CHANNEL 1

Source	SS	df	MS	f
Between Subjects	98.66	17		
Within Subjects	68.67	36		
Trials	6.77	2	3.39	1.86
Residual	61.90	34	1.82	
TOTAL	167.33	53		

APPENDIX 24

SUMMARY OF ANALYSIS OF VARIANCE
COMPLEXITY OF SECONDARY COMPLEX - CHANNEL 2

Source	SS	df	MS	f
Between Subjects	68.76	17		
Within Subjects	142.00	36		
Trials	11.59	2	5.80	1.51
Residual	130.41	34	3.84	
TOTAL	210.76	53		

APPENDIX 25

SUMMARY OF ANALYSIS OF VARIANCE
COMPLEXITY OF SECONDARY COMPLEX - CHANNEL 3

Source	SS	df	MS	f
Between Subjects	66.54	17		
Within Subjects	86.00	36		
Trials	5.48	2	2.74	1.16
Residual	80.52	34	2.37	
TOTAL	152.54	53		

APPENDIX 26

SUMMARY OF ANALYSIS OF VARIANCE
COMPLEXITY OF SECONDARY COMPLEX - CHANNEL 4

Source	SS	df	MS	f
Between Subjects	81.93	17		
Within Subjects	71.33	36		
Trials	.70	2	.35	.17
Residual	70.63	34	2.08	
TOTAL	153.26	53		

APPENDIX 27

SUMMARY OF ANALYSIS OF VARIANCE
COMPLEXITY OF AFTER DISCHARGE - CHANNEL 1

Source	SS	df	MS	f
Between Subjects	155.33	17		
Within Subjects	218.00	36		
Trials	32.33	2	16.17	2.96
Residual	185.67	34	5.46	
TOTAL	373.33	53		

APPENDIX 28

SUMMARY OF ANALYSIS OF VARIANCE
COMPLEXITY OF AFTER DISCHARGE - CHANNEL 2

Source	SS	df	MS	f
Between Subjects	300.76	17		
Within Subjects	327.33	36		
Trials	27.37	2	13.69	1.55
Residual	299.96	34	8.82	
TOTAL	628.09	53		

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APPENDIX 29

SUMMARY OF ANALYSIS OF VARIANCE
COMPLEXITY OF AFTER DISCHARGE - CHANNEL 3

Source	SS	df	MS	f
Between Subjects	246.67	17		
Within Subjects	215.33	36		
Trials	19.11	2	9.56	1.66
Residual	196.22	34	5.77	
TOTAL	462.00	53		

APPENDIX 30

SUMMARY OF ANALYSIS OF VARIANCE
COMPLEXITY OF AFTER DISCHARGE - CHANNEL 4

Source	SS	df	MS	f
Between Subjects	236.67	17		
Within Subjects	179.33	36		
Trials	27.44	2	13.72	3.07
Residual	151.89	34	4.47	
TOTAL	416.00	53		

APPENDIX 31

SUMMARY OF ANALYSIS OF VARIANCE
LATENCY TO PEAK DEFLECTION - CHANNEL 1

Source	SS	df	MS	f
Between Subjects	55630.09	17		
Within Subjects	35466.67	36		
Trials	695.37	2	347.69	.34
Residual	34771.30	34	1022.69	
TOTAL	91096.76	53		

APPENDIX 32

SUMMARY OF ANALYSIS OF VARIANCE
LATENCY TO PEAK DEFLECTION - CHANNEL 2

Source	SS	df	MS	f
Between Subjects	36163.64	17		
Within Subjects	73760.67	36		
Trials	185.03	2	92.52	.04
Residual	73575.64	34	2163.99	
TOTAL	109924.31	53		

APPENDIX 33

SUMMARY OF ANALYSIS OF VARIANCE
LATENCY TO PEAK DEFLECTION - CHANNEL 3

Source	SS	df	MS	f
Between Subjects	20870.83	17		
Within Subjects	66750.00	36		
Trials	4852.77	2	2426.39	1.33
Residual	61897.23	34	1820.51	
TOTAL	87620.83	53		

APPENDIX 34

SUMMARY OF ANALYSIS OF VARIANCE
LATENCY TO PEAK DEFLECTION - CHANNEL 4

Source	SS	df	MS	f
Between Subjects	55687.04	17		
Within Subjects	51933.33	36		
Trials	1362.04	2	681.02	.46
Residual	50571.29	34	1487.39	
TOTAL	108620.37	53		

APPENDIX 35

SUMMARY OF ANALYSIS OF VARIANCE
AMPLITUDE OF PRIMARY COMPLEX - CHANNEL 1

Source	SS	df	MS	f
Between Subjects	1556.60	17		
Within Subjects	4117.33	36		
Trials	318.82	2	109.41	95
Residual	3898.51	34	114.66	
TOTAL	5673.93			

APPENDIX 36

SUMMARY OF ANALYSIS OF VARIANCE
AMPLITUDE OF PRIMARY COMPLEX - CHANNEL 2

Source	SS	df	MS	f
Between Subjects	2420.16	17		
Within Subjects	8462.67	36		
Trials	939.11	2	469.56	2.12
Residual	7523.56	34	221.28	
TOTAL	10882.83	53		

APPENDIX 37

SUMMARY OF ANALYSIS OF VARIANCE
AMPLITUDE OF PRIMARY COMPLEX - CHANNEL 3

Source	SS	df	MS	f
Between Subjects	2205.92	17		
Within Subjects	4146.67	36		
Trials	827.26	2	413.63	4.24*
Residual	3319.41	34	97.63	
TOTAL	6352.59	53		

*$p < .05$

APPENDIX 38

SUMMARY OF ANALYSIS OF VARIANCE
AMPLITUDE OF PRIMARY COMPLEX - CHANNEL 4

Source	SS	df	MS	f
Between Subjects	16514.83	17		
Within Subjects	29200.00	36		
Trials	376.33	2	188.17	.22
Residual	28823.67	34	847.76	
TOTAL	45714.83	53		

APPENDIX 39

SUMMARY OF ANALYSIS OF VARIANCE
SECONDARY COMPLEX - LATENCY TO BEGINNING - CHANNEL 1

Source	SS	df	MS	f
Between Subjects	14396.76	17		
Within Subjects	15100.00	36		
Trials	423.15	2	211.58	.49
Residual	14676.85	34	431.67	
TOTAL	29496.76	53		

APPENDIX 40

SUMMARY OF ANALYSIS OF VARIANCE
SECONDARY COMPLEX - LATENCY TO BEGINNING - CHANNEL 2

Source	SS	df	MS	f
Between Subjects	8385.65	17		
Within Subjects	11550.00	36		
Trials	950.93	2	475.47	1.53
Residual	10559.07	34	311.74	
TOTAL	19935.65	53		

APPENDIX 41

SUMMARY OF ANALYSIS OF VARIANCE
SECONDARY COMPLEX - LATENCY TO BEGINNING - CHANNEL 3

Source	SS	df	MS	f
Between Subjects	10075.92	17		
Within Subjects	5616.67	36		
Trials	84.26	2	42.13	.26
Residual	5532.41	34	162.72	
TOTAL	15692.59	53		

APPENDIX 42

SUMMARY OF ANALYSIS OF VARIANCE
SECONDARY COMPLEX - LATENCY TO BEGINNING - CHANNEL 4

Source	SS	df	MS	f
Between Subjects	9468.98	17		
Within Subjects	9983.33	36		
Trials	1195.37	2	597.69	2.31
Residual	8787.96	34	258.47	
TOTAL	19452.31	53		

APPENDIX 43

TESTS ON DIFFERENCES BETWEEN TOTALS
AMPLITUDE OF AFTER DISCHARGE - CHANNEL 1

Ordered Measures		Control	6 Mo.	12 Mo.
	TOTALS	306	383	609
Control	306	---	77	303*
6 Mo.	383		---	226*
12 Mo.	609			---
Truncated Range r			2	3
q.95 (r, 30)			2.89	3.49
$\sqrt{nMSres}$ q95 (r, 30)			206.37	249.22

*p<.05

APPENDIX 44

TESTS ON DIFFERENCES BETWEEN TOTALS
AMPLITUDE OF PRIMARY COMPLEX - CHANNEL 3

Ordered Measures		Control	6 Mo.	12 Mo.
	TOTALS	268	404	428
Control	268	---	136*	230*
6 Mo.	404		---	24
12 Mo.	428			---
Truncated Range r			2	3
q.95 (r, 30)			2.89	3.49
$\sqrt{nMSres}$ q95 (r, 30)			83.84	125.76

*p<.05

APPENDIX 45

TESTS ON DIFFERENCES BETWEEN TOTALS
COMPLEXITY OF PRIMARY COMPLEX - CHANNEL 1

Ordered Measures		Control	6 Mo.	12 Mo.
TOTALS		44	62	68
Control	44	--	18*	24*
6 Mo.	62		--	6
12 Mo.	68			--
Truncated Range r			2	3
q.95 (r, 30)			2.89	3.49
$\sqrt{nMSres}$ q95 (r, 30)			17.49	21.66

*p<.05

APPENDIX 46

TESTS ON DIFFERENCES BETWEEN TOTALS
WIDTH OF SECONDARY COMPLEX - CHANNEL 1

Ordered Measures		6 Mo.	Control	12 Mo.
TOTALS		2645	2925	2940
6 Mo.	2645	----	280*	295*
Control	2925		----	15
12 Mo.	2940			----
Truncated Range r			2	3
q95 (r, 30)			2.89	3.49
$\sqrt{nMSres}$ q95 (r, 30)			210.31	253.97

*p<.05

APPENDIX 47

TESTS ON DIFFERENCES BETWEEN TOTALS
AMPLITUDE OF SECONDARY COMPLEX - CHANNEL 3

Ordered Measures		6 Mo.	Control	12 Mo.
	TOTALS	689	763	1140
6 Mo.	689	---	74	451*
Control	763		---	377*
12 Mo.	1140			---
Truncated Range r		2	3	
q95 (r, 30)		2.89	3.49	
$\sqrt{nMSres}$ q95 (r, 30)		354.74	428.39	

*p<.05

APPENDIX 48

TESTS ON DIFFERENCES BETWEEN TOTALS
AMPLITUDE OF SECONDARY COMPLEX - CHANNEL 1

Ordered Measures		6 Mo.	Control	12 Mo.
	TOTALS	579	737	1481
6 Mo.	579	---	158	902*
Control	737		---	744*
12 Mo.	1481			---
Truncated Range r		2	3	
q95 (r, 30)		2.89	3.49	
$\sqrt{nMSres}$ q95 (r, 30)		583.42	704.1	

*p<.05

APPENDIX 49

TESTS ON DIFFERENCES BETWEEN MEANS
AMPLITUDE OF SECONDARY COMPLEX - CHANNEL 2

Ordered Measures	Control	6 Mo.	12 Mo.
TOTALS	544	614	1096
Control 544	---	70	552*
6 Mo. 614		---	482*
12 Mo. 1096			----
Truncated Range r	2	3	
q.95 (r, 30)	2.89	3.49	
$\sqrt{nMSres}$ q95 (r, 30)	419.56	506.67	

*p<.05